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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2005

THURSDAY, APRIL 1, 2004

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

The subcommittee met at 9:30 a.m., in room SH–216, Hart Senate Office Building, Hon. Arlen Specter (chairman) presiding.

Present: Senators Specter, Cochran, Stevens, and Harkin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF ELIAS A. ZERHOUNI, M.D., DIRECTOR

ACCOMPANIED BY:

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OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Good morning, ladies and gentlemen. The time is precisely 9:30, which is our starting time, and the Appropriations Subcommittee on Labor, Health, Human Services, and Education will now proceed.

Today we will consider the appropriations process as it applies to the National Institutes of Health. And as I have stated on many occasions, I consider NIH the crown jewel of the Federal Government. It may be the only jewel of the Federal Government.

But medical science and humanity is deeply indebted to the extraordinary work which has come out of medical research from the National Institutes of Health.

The budget process is always complicated and a goal was established to double NIH funding, which we have more than met. When asked what would happen after doubling, as you know, my response was instantaneous and obvious, and it was tripling. It would be too hard to quadruple it before you triple it.

When I took over the chairmanship of this subcommittee in January 1995, I took a look at the priorities and thought this was none higher, really at the top of the list. And Senator Harkin, the ranking member, agrees. We know around here if you want to get something done, you have to cross party lines. Sometimes it gets you into trouble if you have a primary election campaign. My opponent thinks I should not talk to Democrats. But Senator Harkin and I, when we have changed the gavel, it has been seamless and we have proceeded to give tremendous support to NIH.

We have a very tight discretionary budget this year. It is up one-half of 1 percent, and that is very, very, very difficult. The administration has put in a figure of $729 million over the $28.5 billion

budget, and as I am sure you know, we offered an amendment to increase it by $1.3 billion and we were successful, 72 to 24.

But there were some strenuous arguments raised by my colleagues in the Senate that NIH was getting too much funding compared to other important research Departments in the Federal Government. And when one of my colleagues made an impassioned plea, I agreed with him that the other Departments were not getting adequate funding. But that did not bear on not adequately funding NIH. And what it takes is the subcommittee chairmen to pick up those important research projects and take the lead and get them funded.

We have a Federal budget of $2,400,000,000,000. Do you know how much money that is? Well, nobody else does either.

They say if you took a room this size, it would be insufficient to stuff $10,000 bills into it.

We can afford money for research. That is the best investment that we are making beyond any question. But it is a fight.

NIH has its own problems which you know about, challenges on conflicts of interest, which we have addressed in a separate hearing and we will talk about today, the issues about compensation, an issue which I know is being addressed.

NIH is being attacked on an ideological level. The November 28, 2003 edition of Science had an editorial marked Don't Let Ideology Trump Science. An amendment was offered in the House of Representatives to strike four NIH grants because sex was mentioned in the title, peer-reviewed. One of them involved a question of spread of venereal disease at truck stops where truckers are highly vulnerable, long stops, fatigue, away from home, places frequented understandably by prostitutes, and NIH wanted to make a study. And that and three other of your projects were challenged because if you have sex in the title, it makes a good 30-second commercial, if you voted for it, to defeat you. The surprising thing was that in the House of Representatives the amendment almost passed: 212 to 210.

Now, it just happens that the amendment was offered by the fellow who wants to take my seat on the U.S. Senate who has voted against every domestic spending bill, voted against Head Start, voted against Medicare reform, voted against the budget for Labor, Health and Human Services, voted against the budget for NIH. So in this town you have to be prepared to defend yourself against attacks. So if you have one or two, Dr. Zerhouni, do not think you are being discriminated against.

It goes with the territory. I think it is within your pay grade to defend yourself, Dr. Zerhouni, and to prevail, and I think it is within my pay grade to prevail also. But it is a battle.

So much for an opening statement. I read it just like Betty Lou wrote it for me.

Super Senator Taylor. She is not just a regular Senator. She is a super Senator.

Dr. Elias Adam Zerhouni began his tenure as the 15th Director of NIH on May 20, 2000. He had a very distinguished career prior to coming to NIH: executive vice dean of Johns Hopkins University School of Medicine, Chair of the Department of Radiology; Martin Donner Professor of Radiology; medical degree from the University

of Algiers School of Medicine; and residency in diagnostic radiology at Johns Hopkins. Thank you for joining us, Dr. Zerhouni, and we look forward to your testimony.

SUMMARY STATEMENT OF DR. ELIAS ZERHOUNI

Dr. ZERHOUNI. Thank you, Mr. Chairman. It is our pleasure to be here with the 27 institute and center directors of NIH to present our budget, but also to express our thanks and appreciation for your strong leadership on behalf of research and medical research and NIH.

INTRODUCTION OF NEW INSTITUTE DIRECTORS

I would like to start by introducing three of our new directors, and I will ask them to stand up to be introduced to you, Mr. Chairman.

Dr. Story Landis is now the Director of the National Institute of Neurological Diseases. She has been appointed in the past year and has done an outstanding job already working with all aspects of neurological disorders, including collaboration with patient groups in trying to find the best approaches to rising threats of neurological degenerative diseases.

Dr. Nora Volkow is the new Director of the National Institute of Drug Abuse. She has joined us from the Brookhaven National Laboratory in Stony Brook University. She is a leader in imaging of drug addiction and has already changed the strategy of her institute in many appropriate ways.

Dr. Jeremy Berg is the new Director of the National Institute of General Medical Sciences. Dr. Jeremy Berg joined us from Johns Hopkins where he was the Chair of the Basic Science Institute at Johns Hopkins and Chair of the Department of Biophysics.

I also would like to mention two acting Directors, Dr. Barbara Alving, who is the acting Director of NHLBI, and Dr. Sharon Hrynkow, who is the acting Director of the Fogarty International Center.

BREAKTHROUGHS AND ADVANCES

Mr. Chairman, members of the committee, it is my pleasure to actually summarize the written testimony that we submitted to you. What I would like to do is go right away and tell you how important your investment has been in terms of specific breakthroughs and advances between last year and this year.

NIH developed a completely new Ebola vaccine that can protect the population in less than a month. This a real breakthrough in biodefense.

Just 2 days ago, NIAID announced that a new SARS experimental vaccine has been successful in animal experiments and will enter human trials as soon as we can do so. This is less than a year after the SARS epidemics which we knew not the cause of and it took us several weeks to find the cause. A year later, we are ready to fight this disease if it reappears.

We discovered in 2003 several genes, for the first time, associated with schizophrenia. This was ranked as the number two ad-

vanced scientific advance of 2003, following the discovery of dark matter in the universe.

We identified just 3 weeks ago a new master switch gene relating to type 2 diabetes. This is a very important discovery that will help us in discovering how type 2 diabetes develops.

We have changed the practice paradigm of long-term hormone replacement therapy for women because of the landmark studies of the Women's Health Initiative.

Today on the cover of Nature magazine, we are announcing the completion of the rat genome, a very important advance. As you know, by 2005 we were hoping to only have the human genome available to us. We now have the mouse, the rat, and the human genome, and we will be able to do comparative analysis that will advance our understanding of biology and disease.

NIH ROADMAP FOR MEDICAL RESEARCH

All throughout the past 2 years, we have also taken into account the need for new science strategies, and this is what we call the NIH roadmap for medical research. The roadmap is essentially our effort to find ways to accelerate basic research discoveries and speed the translation of those discoveries into clinical practice. It is a dedicated effort to explicitly address roadblocks that slow the pace of medical research in improving the health of the American people.

The major driver for this approach is exemplified on this slide in front of you, and that is that we need to transform medical research in the 21st century. In the 20th century, we treated disease when symptoms appeared and normal function had been lost. Why was that? Because for the past 5,000 years and the 20th century included, we did not understand the molecular and cellular events that led to disease. So we had to wait until the disease was explicit. And this is very expensive in both financial and disability costs.

The paradigm of the 21st century is that we will intervene before symptoms appear and preserve normal function for as long as possible because we do understand much better the genetic events that lead to disease.

We have come up with very bold initiatives. We will integrate all clinical research networks that are under NIH throughout the country and link them to community physicians to form new communities of research that will translate much quicker, much more efficiently than we have in the past the benefits of our fundamental understanding of research.

A good example is juvenile rheumatic diseases, a disease set that affects only 300,000 children in the country. To do good research and have enough understanding of what happens, we need to recruit patients across the Nation, and this will be facilitated by a project of the roadmap called National Clinical Research Networks with trained community physicians in every community linked to academic centers.

We continue to invest across NIH in a combined and coordinated fashion to advance medical research as fast as we can. This year we are requesting $237 million for the roadmap.

STEWARDSHIP

We have continued also to focus on management excellence and stewardship of our resources. Let me point out two very simple statistics. Our funding went up by 141 percent in the past 10 years, almost 2 and a half times, 2.4 times. Our FTE's, the number of people, at NIH needed to manage this portfolio has only increased by 16 percent. Why? Because we have aggressively used modern methods of management using information systems to prevent the need for us to increase our FTE numbers. Our Research Management and Support budget has gone from 4 percent of our budget to 3.5 percent of our budget. So we are doing what you are asking us to do and being very good stewards.

As you said, we will have on May 6 a final meeting of the Advisory Committee to the Director to finalize the recommendations of the Blue Ribbon Panel for conflict of interest and will report back to you as soon as we have that.

FISCAL YEAR 2005 BUDGET REQUEST

Mr. Chairman, we are requesting a budget of $28.607 billion which is $28.527 billion from this committee, and a 2.6 percent increase over 2004. We also have at our program level $47 million for nuclear and radiological countermeasures which are housed in the Public Health Service emergency fund.

PREPARED STATEMENT

We are pleased to be here and will answer any of your questions. Again, we would like to thank the bipartisan support of this committee over the years. Thank you, Mr. Chairman.

[The statements follow:]

PREPARED STATEMENT OF DR. ELIAS A. ZERHOUNI

Good morning, Mr. Chairman and members of the Committee. Let me begin by expressing my deepest appreciation to the Congress, Secretary Thompson, President Bush, and the American people for their generous and bipartisan support of the NIH's efforts to help improve the health of all our citizens. I respect the extraordinary effort of this committee and, Mr. Chairman, your leadership as well. I thank you for it.

The year 2004 marks a sea change for the NIH and its Roadmap for Medical Research. We are refining our basic and clinical research programs to ensure that new discoveries rapidly lead to new and improved diagnostics, treatments and prevention strategies that extend the length and improve the quality of human life.

In my testimony today, I want to cover four areas: first, highlight several key research advances that took place in the last year which represent the critical contributions of NIH intramural researchers and grantees; second, give examples of how the NIH Roadmap effort will help shape our approach to patient-oriented research; third, offer examples of our stewardship; and fourth, present an overview of our budget. In the course of my testimony, I will mention emerging priorities and our plans for responding to the health challenges ahead.

BREAKTHROUGHS & ADVANCES

Each year, the public investment in research yields critical scientific advances. The four I highlight here are just a sample of the many that represent the development of new and improved treatments, diagnostics, or prevention strategies that will affect the health of the entire nation.

Few viruses are feared more than the Ebola, a deadly microbe that causes outbreaks in Africa and Asia and kills up to 90 percent of those it infects. Scientists at the NIH National Institute of Allergy and Infectious Diseases Vaccine Research

Center developed a single dose, fast-acting, experimental Ebola vaccine that successfully protects monkeys after just one month, and human trials are now under way.

This year NIH research further elucidated the role of widely used hormone replacement therapies. The NIH halted the estrogen alone study of the Women's Health Initiative on March 1, 2004 after 5.6 years of follow-up, due to increased risk of stroke. You will recall that NIH, in 2002, stopped the combination hormone trial arm of the Women's Health Initiative early due to an increased risk of invasive breast cancer, coronary heart disease, stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo. It indicated that healthy postmenopausal women taking combination hormone therapy also suffered twice the rate of dementia as those taking a placebo. Together, the results of these clinical studies changed conventional dogma, and provided important new evidenced-based information to women who are deciding whether to begin or how long to continue menopausal hormone therapy. These trials clearly are having a major impact on the health of people we know and love—our wives, our sisters, our daughters and our mothers.

The third advance was the discovery of genes associated with schizophrenia, which is a profoundly disabling disorder that affects one percent of the adult population. It is marked by hallucinations, delusions, social withdrawal, flattened emotions, and loss of social and personal care skills.

Research like this on the genetics of mental illness was named the Number 2 scientific "breakthrough of the year" for 2003 by the prestigious peer-reviewed journal, Science. Most of this work was funded by NIH and included discoveries of candidate genes for schizophrenia, depression, anxiety and bipolar disorders. These discoveries bring us closer to developing new diagnostic tests, strategies for prevention, and targets for the treatment of schizophrenia and other mental disorders.

The fourth advance came only three weeks ago, when NIH announced a major new discovery, the identification of a common variation of a pancreatic "master switch" gene that increases the risk of type 2 diabetes by 30 percent. Type 2 diabetes now affects 17 million people in the United States, and is responsible for enormous health care costs. This gene discovery opens the door to the development of new and more effective methods of prevention and treatment.

NIH ROADMAP

Let me now turn your attention to the NIH Roadmap for Medical Research. I want to tell you why the Roadmap is so important to the future of medical research and to innovations in improving people's health. I also want to give you some examples of how we at NIH expect the Roadmap to change the way we do research and the practice of medicine.

One of the questions we face is how do we successfully do our part in the battle to contain health costs? We need to address the following issues: What are the roadblocks? What are the major challenges? How can we most effectively invest the funds that the American taxpayers entrust to us to fashion the fastest track to discovery as well as translate those discoveries to the patient's bedside or the doctor's office?

In seeking answers to these questions, one thing becomes clear. The traditional paradigm of medical care—when practitioners waited for the disease to cause the patient the loss of some function—must be replaced by a paradigm where health professionals act before the individual loses any function. This has become even more critical since chronic diseases now consume about 75 percent of our fast-growing health care expenditures.

Let me present four examples of how the NIH Roadmap will transform our approach to biomedical research in specific disease areas.

The first example is schizophrenia, a disorder that—as I mentioned earlier—affects one percent of the U.S. population. The peak onset occurs between the ages of 18 and 25. Schizophrenia has the hallmarks of both a neurodevelopmental and a neurodegenerative disease. But after 100 years of neuropathological study, we still lack knowledge of the precise cause of the disorder.

Today, schizophrenia is the fifth leading cause of years lost due to disability among Americans from ages 15–44. Although we can treat the so-called "positive" symptoms, such as hallucinations and delusions, we do not yet have treatments for the "negative" symptoms, like withdrawal and cognitive deficits. And these are the largest source of disability.

Less than 30 percent of people with this illness are currently employed. And people with schizophrenia represent one of the largest groups on atypical antipsychotics as the treatment of choice. In 2001, Medicaid paid for more than 50 percent of the

total spending on atypical antipsychotics, amounting to $2.7 billion, a figure which has been growing at roughly 25 percent a year for the past 3 years.

Today, we lack a diagnostic test or a strategy for preventing schizophrenia. This situation is similar to cardiovascular disease 30 years ago in that we see schizophrenic patients only after their first "heart attack," that is, episode, and we do not have the equivalent of cholesterol as an identifiable risk factor.

However, what we have done recently—and what holds great promise for those who are suffering—is identify 12 genes associated with risk. Our challenge now is to move from the discovery of those genes—most of which have no known function—to understand the role these genes play in the onset and progression of this brain disease—and do something about it.

Our hope is to use these genes to identify what is abnormal in the brains of schizophrenics, identify it early and thus provide the psychiatric equivalent of serum cholesterol. To accomplish this, we must study the protein products of these genes by using molecular tools that can make their function transparent.

It is precisely here that the NIH Roadmap will help accelerate the effort to study protein products through so-called molecular libraries—databases of information on small molecule compounds like aspirin and antihistamines. These libraries will let researchers screen hundreds of thousands of small molecules to yield these tools.

For example, we know that a variation in the neuregulin gene is associated with an increased risk for schizophrenia. To understand how this gene confers risk, we need to find chemicals that mimic or inhibit the gene's function. This would give us a precise description of how alterations in the gene change the activity of brain cells. Molecular libraries will not only yield the tools to study the neuregulin gene but also provide a test for vulnerability to schizophrenia. With such tools and tests, doctors could approach risk for schizophrenia the way we currently approach risk for heart disease.

A second example where the NIH Roadmap offers promise is in pediatric diseases, through the creation of clinical research networks.

Uncommon disorders like the juvenile forms of rheumatic diseases, such as arthritis, lupus and dermatomyositis, affect 300,000 children in the United States. Not one of these diseases is common enough to be studied intensively at any one academic health center. Thus, many such centers as well as community-based pediatricians are needed to collect a sufficient group of patients who can participate in these studies to gather meaningful results.

The development of clinical research networks that focus on chronic childhood diseases—like those already established for childhood cancers—and the potential to include community physicians trained in clinical research methodology in the research process will enable clinical trials to be more efficient and effective.

Using the NIH Roadmap clinical research networks concept, this could occur without building a new, and often very expensive, infrastructure for every new trial. Including community-based pediatricians as full partners in the research will allow us to overcome some of the limitations of patient recruitment that we currently experience and enable more children to participate in these trials, and accelerate the development of new treatments.

The third example is Alzheimer's Disease (AD). We have made considerable progress in understanding Alzheimer's Disease. Fifteen years ago, we knew none of the genes that cause AD and we had only a limited understanding of the biological pathways involved in the development of brain pathology. Ten years ago, we could not model the disease in animals. Five years ago, we were not funding any prevention trials and had no way of identifying persons at high risk for the disease. And, as recently as one year ago, we had no way of imaging AD's characteristic amyloid plaques in a living person.

Today, we can do all of these things. And we are poised to make the discoveries that will transform our understanding of the basic and clinical aspects of AD and enable us to effectively prevent, diagnose, and treat it using several NIH Roadmap initiatives.

Through basic research in Alzheimer's disease, we identified a number of brain pathways that are potential targets for preventive interventions. These range from dysfunction and death of specific neurons to loss of the connections between neurons. Roadmap efforts to improve imaging of small molecules will let us visualize the effects of treatments more rapidly and accurately, which could make effective AD clinical trials smaller, faster and more affordable.

My fourth and final example is cardiovascular disease. One of the greatest public health success stories of the last half century is the dramatic reductions in mortality from cardiovascular diseases. Studies initiated by the NIH—the Framingham Heart Study and the Lipid Research Clinics Coronary Primary Prevention Trial—have been key to that success. They helped not only to identify risk factors that con-

tribute to the development of cardiovascular diseases, but also to demonstrate the efficacy of therapeutic interventions to control them.

Even so, cardiovascular disease remains an enormous health burden, accounting for 38 percent of all deaths in the United States in 2001. Progress in reducing that burden will require continued efforts to refine our understanding of risk factors, such as obesity and high cholesterol, and to identify and evaluate new prevention approaches. This means that large scale population-based studies will remain a critical component of our research effort.

The NIH Roadmap will help fashion the interactive network and involvement of many community-based practitioners. For example, we can make better use of large-scale organizations set up for single studies, such as the recently completed Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Instead of disbanding it, we can involve many or all of the investigators in other trials addressing not only cardiovascular disease but also other diseases. The National Electronic Clinical Trials and Research (NECTAR) initiative—a critical part of the Roadmap effort to re-engineer clinical research—will enable data sharing and enhance comparison and aggregation of results from multiple trials by using standard definitions of outcomes and adverse events. In the future, patients will know directly from their own community doctors, who will be equipped with the new web-based NECTAR, what medical research can do for them in terms of participation in studies, the best available therapies, and nearby advanced research centers.

STEWARDSHIP

We realize that to advance the NIH scientific agenda, our management and administration must be effective, efficient and productive. By introducing new information technology and business systems and streamlining governance structures, we are placing continuous improvement of management and administrative functions at the forefront of our agency priorities. Let me highlight a few of our efforts.

NIH is making rapid progress to modernize its business and financial systems. An agency-wide information technology system, known as the New Business System (NBS), is integrating such processes as acquisitions, travel, property, and financial management. This effort will reduce the cost and complexity of doing business, enhance the level of service, and improve management controls.

NIH is also improving its peer review system, which is recognized as the cornerstone of NIH's success. The NIH Center for Scientific Review (CSR), the focal point of the NIH peer review system, reviews about 70 percent of the grant applications submitted to NIH. In fiscal year 2003, CSR received a record-breaking 66,000 grant applications.

CSR is in the final stages of crafting new and more flexible review panels organized into 24 scientifically-related clusters. NIH is also incorporating new technologies into the review process through the electronic Research Administration (eRA). The goal is to implement an end-to-end electronic grants administration for NIH research award mechanisms that could reduce the waiting period from submission of an application to a grant award by more than two months—from 9 to 10 months down to 7 months.

Remarkably, because of improvements in productivity over the past ten years, NIH funding has grown 141 percent, while our FTEs have increased by only 16 percent.

The NIH also realizes the need for a more efficient means of trans-NIH coordination. To streamline decision making, we reduced the plethora of NIH administrative committees down to a trans-NIH Steering Committee and 5 working groups. Additionally, as we discussed when I met with the subcommittee in January, all our conflict of interest policies and procedures are under review both to ensure that they meet the highest standards and, most importantly, to preserve the public's trust in the NIH. I will soon receive the report of a Blue Ribbon Panel I created to advise NIH on what changes they think we should make. I will inform you about their conclusions, and mine, once they complete their work next month.

BUDGET

The discretionary fiscal year 2005 budget request for the NIH is $28,607 million ($28,527 million from this subcommittee and $80 million from the VA/HUD subcommittee), an increase of $729 million or 2.6 percent over the fiscal year 2004 Enacted Level. In addition, $47.4 million is included in the budget authority request of the Public Health and Social Services Emergency Fund (PHSSEF), for NIH research in radiological/nuclear countermeasures, and $150 million in mandatory funds was previously appropriated for the Special Type 1 Diabetes Initiative, bring-

ing NIH's program level total to $28,805 million, or a 2.7 percent increase. The budget increases funding for the NIH Roadmap (+$109 million), obesity research (+$40 million), which will thus grow by 10 percent from $400 million in 2004, and biodefense research (+$74 million), an increase of 4.5 percent over fiscal year 2004.

CONCLUSION

In conclusion, I want to reemphasize the NIH commitment to help improve the health of the American people. Although we have had great success in changing acute lethal diseases like AIDS and many cancers and childhood diseases into chronic manageable diseases, there are many challenges ahead. Life expectancy has increased and the diseases of aging and the aging population have become major priorities.

With a shift from acute to chronic diseases, health disparities and pediatric diseases also present challenges, as do emerging and re-emerging diseases, such as SARS. We are confident, as the committee has shown it is, that medical research will make a critical difference in the lives of all Americans.

As the NIH director, I fully understand and embrace my role as the steward of our Nation's investment in medical discovery. And I remain vigilant to ensure that these precious resources—including over 212,000 scientists working at 2,800 institutions in the United States and overseas and the 5,000 scientists at the NIH itself—are used wisely and efficiently and produce not only new knowledge but also tangible benefits that touch the lives of every individual who reaches out for our help.

BUILDINGS AND FACILITIES PROGRAM

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the Buildings and Facilities (B&F) Program for fiscal year 2005, a sum of $99,500,000.

ROLE IN THE RESEARCH MISSION

State-of-the-science research and support facilities are a vital part of the research enterprise. The National Institutes of Health's (NIH) Buildings and Facilities (B&F) program designs, constructs, repairs and improves the agency's portfolio of laboratory, clinical, animal, administrative and support facilities at its six installations in three states. These facilities house researchers from the NIH Institutes' and Centers' (ICs) intramural basic, translational, and clinical research programs; the NIH leadership, and various programs that support agency operations. The fiscal year 2005 B&F budget request supports critically needed and timely investments to keep the agency's facilities and supporting physical infrastructure healthy, safe, secure, and research ready.

The B&F budget request is the product of a comprehensive, corporate capital facilities planning process. This process begins with extensive consultation across the research community and the NIH's professional facilities staff. It works through the Facilities Working Group, an advisory committee to the NIH Steering Committee and the HHS Capital Investment Review Board. The budget request is the current year plan in a rolling five-year facilities plan. Through this process, the real and insistent program demand for more effective and efficient facilities designed to support current and emerging investigative techniques, technologies, and tools is integrated with, and balanced against, the need to repair, renovate, and improve the existing building stock to keep it in service and to optimize its utility.

The fiscal year 2005 request provides the necessary funding support for the ongoing safety, renovation and repair, and related projects that are vital to proper stewardship of the entire portfolio. It provides funds to continue the functional integration of the clinical research components of the existing Building 10 with the new Mark O. Hatfield Clinical Research Center (CRC). Additionally, the request includes funds to: complete the design of the Animal Research Center (ARC) on the Bethesda campus; complete the creation of a security buffer around the Rocky Mountain Laboratories (RML), in Hamilton, MT; and to add another chiller to the NIH's Bethesda campus central utility system that is needed to meet current and anticipated cooling demands.

The fiscal year 2005 B&F budget request is organized among five broad Program Activities: Construction, Essential Safety and Regulatory Compliance, Repairs and Improvements, Renovations, and Equipment/Systems. The fiscal year 2005 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 facilities planning process and are the NIH's capital facility priorities for fiscal year 2005.

FISCAL YEAR 2005 BUDGET SUMMARY

The fiscal year 2005 budget request for Buildings and Facilities is $99.5 million. The B&F request contains $16.5 million for Construction, including $5 million to complete the design of an Animal Research Center; $9.5 million to complete the creation of a security buffer around the Rocky Mountain Laboratories (RML) in Hamilton, MT; and $2 million for concept development studies of projects proposed in the facilities plan.

There is a total of $6 million for Essential Safety and Regulatory Compliance programs composed of $0.5 million for the phased removal of asbestos from NIH buildings; $2 million for the continuing upgrade of fire and life safety deficiencies of NIH buildings; $1 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 $2 million for the continued support of the rehabilitation of animal research facilities. In addition, the fiscal year 2005 request includes $59.2 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. The request includes $10.8 million in Renovations to complete the Building 10 Transition Program. Finally, the request includes $7 million in Equipment/Systems for the Chiller 27 project.

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

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 2005. This budget includes $671.6 million, an increase of $18.8 million over the fiscal year 2004 enacted level of $652.7 million comparable for transfers proposed in the President's request. As the Director of the NEI, it is my privilege to report on the 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.

RETINAL DISEASES

Retinal diseases are a diverse set of sight-threatening conditions that include age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinitis pigmentosa, Usher's syndrome, ocular albinism, retinal detachment, uveitis (inflammation), and cancer (choroidal melanoma and retinoblastoma). One of the most tragic retinal diseases, retinopathy of prematurity (ROP), causes severe vision loss in premature, low-birthweight infants. ROP is characterized by excessive growth of abnormal blood vessels in the back of the eye that often hemorrhage and scar the retina. This year, results from an NEI-funded clinical trial, called the Early Treatment of Retinopathy of Prematurity (ETROP), established that early treatment, based on newly developed diagnostic criteria, improves visual outcomes in infants at the greatest risk of developing ROP. The ETROP study also found that these new diagnostic criteria were helpful in select patient subgroups that may not ultimately develop ROP. For these infants, careful observation was found to be the best approach. Results from ETROP will greatly improve visual outcomes for children with ROP.

Age-related macular degeneration (AMD) is a leading cause of blindness in patients over age 60 in the United States and is a major health problem in most other developed countries. More than 9 million Americans have some degree of AMD (Archives of Ophthalmology, In Press). Based on the results of an NEI-funded clinical trial, the Age-Related Eye Diseases Study (AREDS), 1.3 million of these people would develop advanced AMD if no treatment were given to reduce their risk. If these people at risk for development of advanced AMD received the supplements (vitamins C, E, beta-carotene, and zinc) used in AREDS, more than 300,000 of them would avoid advanced AMD and any associated vision loss over the next five years. Delaying the advance of a disease in older-age populations is an essential strategy to reduce the burden and incidence of disease.

Uveitis is an autoimmune inflammatory disease of the eye that accounts for up to 10 percent of blindness in the United States (Ophthalmology 2004; 111:491–500). In collaboration with researchers at the National Cancer Institute, NEI intramural scientists have reported promising results with the use of a monoclonal antibody (daclizumab) in the long term treatment of patients with uveitis. This new therapy seems to have many fewer side effects than existing immunosuppressive therapies,

leading to an improved quality of life. Planning is underway to begin a Phase III study to evaluate the full potential of this therapy.

CORNEAL DISEASES

The cornea is the transparent tissue at the front of the eye. Corneal disease and injuries are the leading cause of visits to eyecare clinicians, and are some of the most painful ocular disorders. In addition, approximately 25 percent of Americans have a refractive error known as myopia or nearsightedness that requires correction to achieve sharp vision; many others are far-sighted or have astigmatism.

NEI intramural scientists found that serum albumin represents up to 13 percent of the total water-soluble protein of the mouse cornea. Humans also have abundant serum albumin in the corneal stroma. Because the serum albumin accumulates in the corneal stroma by diffusion from the blood supply surrounding the cornea, it may provide an improved route of drug delivery to the cornea. Conjugating serum albumin to the drug of choice and injecting the conjugate into the blood stream will not only direct the drug within the cornea, but extend its half-life within this tissue. Future research will evaluate the usefulness of serum albumin as a drug carrier to treat corneal disorders.

NEI intramural scientists recently identified an enzyme called CDK5 that regulates corneal epithelial cell adhesion and migration. Using a model wound healing system, these researchers found that the rate of wound closure was significantly retarded in cells with too much CDK5 and accelerated in cells in which the CDK5 was inactivated. Continuation of this line of research may provide the means to promote rapid healing of corneal tissues that have been damaged by disease or injury.

CATARACT

Cataract, an opacity of the lens of the eye, interferes with vision and is the leading cause of blindness in developing countries. In the United States, cataract is also a major public health problem. The economic burden of cataract will worsen significantly in coming decades as the American population ages.

Age-related cataract formation is believed to result from the complex effects of aging on normal physiological processes. It has long been recognized that lens transparency is a function of a very high concentration of soluble proteins, the crystallins, within the specialized lens fiber cell. In the lens, α-crystallin has a dual function: it accumulates in fiber cells in high concentrations to produce the high refractive index needed for transparency, and it functions as a molecular chaperone to protect against clouding of the lens due to protein aggregation. For some time, scientists have attempted to understand how α-crystallin can continue to perform its chaperone functions over a range of stress conditions encountered by the lens during a lifetime. New data suggest that under low stress, α-crystallin is maintained in a multi-subunit complex. Under conditions of high stress, α-crystallin breaks into smaller sub-units that can protect the clarity of the lens from protein aggregation. It has been hypothesized that this chaperone function decreases with age and leaves the lens more vulnerable to stressful conditions. Improving our understanding of this protective role of α-crystallin may one day lead to the means to prevent cataract.

GLAUCOMA AND OPTIC NEUROPATHIES

Glaucoma is a group of eye disorders that share a distinct type of optic nerve damage, which can lead to blindness. Elevated intraocular pressure (IOP) is frequently, but not always, associated with glaucoma. Glaucoma is a major public health problem and is a leading cause of blindness in African Americans (Archives of Ophthalmology, In Press).

A hallmark of glaucoma is the death of retinal ganglion cells (RGC) in the retina, which can lead to catastrophic vision loss. Previous NEI studies have found evidence that elevated IOP deprives RGCs of brain-derived neurotrophic factor (BDNF), an endogenous protein that is crucial to RGC survival. Ocular injections of BDNF in rodent models of glaucoma have improved RGC survival. However, due to the relatively short half-life of this protein, the need for frequent ocular injections would not bode well in treating a chronic disease like glaucoma. To overcome this hurdle, NEI-supported researchers recently used gene therapy in rodent models of glaucoma to transfect RGCs with the gene that encodes BDNF, providing a lasting and direct supply of this essential protein. Ongoing NEI-supported laboratory work is evaluating whether gene therapy with BDNF provides long-term benefit and whether gene delivery with other neurotrophic agents, alone or in combination with BDNF, improves RGC survival.

STRABISMUS, AMBLYOPIA AND VISUAL PROCESSING

Developmental disorders such as strabismus (misalignment of the eyes) and amblyopia (commonly known as "lazy eye") are among the most common eye conditions that affect the vision of children. In addition, more than three million Americans suffer from visual processing disorders not correctable by glasses or contact lenses (Archives of Ophthalmology 1990; 108:286–290).

Patching the stronger eye has been a mainstay of amblyopia therapy. Unfortunately, there is no specific patching regimen that is widely accepted for treating the disease. To address the clinical issue of the optimal number of patching hours for moderate amblyopia, an NEI-supported clinical trial compared daily patching of two hours versus six hours for children with moderate amblyopia. Results from this clinical trial revealed that patching the unaffected eye of children with moderate amblyopia for only two hours daily is as effective as patching the eye for six hours. This finding should improve treatment compliance as patching can be a socially stigmatizing and uncomfortable practice for young children.

TECHNOLOGICAL INNOVATIONS

The marriage of computer technology and medical science is creating advances in treating even the most intractable diseases. In one such union, specially designed computer chips implanted in the eye may one day make it possible to partially restore visual function to the blind. Ocular neuro-degenerative diseases such as retinitis pigmentosa (RP) and macular degeneration damage and destroy the light-sensitive photoreceptor cells in the retina. The microelectronic retinal prosthesis, a device developed by NEI-supported researchers, mimics the function of photoreceptor nerve cells by turning light into electric signals. In a recently published study, a 74 year-old patient blind with RP was able to see spots of light, detect motion, and recognize simple shapes. Although preliminary, these results are a promising first step in realizing a prosthetic device that can restore ambulatory vision to patients with retinal degenerative diseases, which are a major cause of vision loss in this country.

PROGRAM INITIATIVES

The rapid progress in areas of gene discovery and bioinformatics has created the need for enhanced cooperation and coordination among groups that provide genetic diagnostic information to the clinician and patient, store and provide DNA specimens to researchers, and maintain data banks of genotype-phenotype information. Such groups are underrepresented in the area of human ocular disease. The purpose of this initiative is to explore the establishment of a national central registry and molecular database of securely coded information from a large number of people with ocular diseases caused by genetic mutations. Information will be provided through a network of cooperating groups who provide genetic and diagnostic services to patients and clinicians. Such a registry and database will be of great value in advancing research for these important diseases.

Clinician scientists will play a major role in translating laboratory findings into safe and effective therapies. However, the vision research community has raised concerns about the future of clinician scientists. Declining clinical revenues are making it increasingly difficult for clinicians to find time away from the examination room to get the training they need. However, many of the investigational therapies now being contemplated will be translated by the next generation of clinician scientists. We need to make sure that current clinician scientists have a capable next generation to pass the torch to.

In addition to its existing extramural training and career development grant programs, the NEI is working to increase the ranks of the clinician scientist through a new intramural clinician scientist training program at the NEI. The Clinician Scientist Development Program is designed for board eligible/certified clinicians who seek to develop an independent research program that integrates the field of vision research with the clinical study of patients with ocular disease or disorders.

The NEI recently published its forward looking *National Plan for Eye and Vision Research.* The NEI's ongoing planning process involves the assessment of important areas of progress in eye and vision research and the development of new goals and objectives that address outstanding needs and opportunities for additional progress. The National Plan can be accessed through the NEI website at: http://www.nei.nih.gov/strategicplanning.

NIH ROADMAP

The NIH Roadmap provides a framework for the priorities the NIH as a whole must address in order to optimize its entire research portfolio. The NEI is committed to the initiatives of the Roadmap and is working to meet its goals. I would like to highlight NEI's involvement in two Roadmap Initiatives: "Nanomedicine" and "Re-Engineering the Clinical Research Enterprise."

The NEI and the National Human Genome Research Institute are heading an NIH committee charged with implementing the Nanomedicine Roadmap Initiative. Nanotechnology originated in the fields of engineering and physics and refers to the research and development of materials and devices at the atomic, molecular or macromolecular levels. Nanomedicine integrates nanotechnology with biomolecular processes. The long-term goal of the Nanomedicine Roadmap Initiative is the development of therapeutic nanotechnology interventions for medical diagnosis and the treatment of disease. To meet these goals we are establishing a process to solicit ideas and concepts germane to the development of Nanomedicine Development Centers.

Nanomedicine Development Centers will be designed to achieve an understanding of biological systems at the nanomolecular level.

Over the past decade NEI-supported laboratory research has given rise to an unprecedented number of promising, pre-clinical therapies for eye disease. NEI's continued success depends on building the clinical infrastructure for translational medicine. Consonant with the NIH Roadmap initiative "Re-engineering the Clinical Research Enterprise" the NEI is creating cooperative clinical research groups that will enhance and expand clinical trial infrastructure. Over the last year, the NEI implemented the Diabetic Retinopathy Clinical Research Network. More than 70 clinical centers with the capability to participate in the clinical trials network have been identified. This network joins the highly effective Pediatric Eye Disease Investigator Group as models for future clinical networks the NEI plans to build.

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. 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 2005, a sum of $196,780,000, which represents an increase of $5,324,000 over the comparable fiscal year 2004 appropriation.

A STRATEGIC APPROACH TO ELIMINATE HEALTH DISPARITIES

Unprecedented scientific advances in biomedical research over the last several decades dramatically improved public health. However, racial and ethnic minorities and other populations that experience disparities in health status have not benefitted equally from our Nation's progress in scientific discovery.

The NIH supports a comprehensive research program to better understand why a broad spectrum of diseases disproportionately impact racial and ethnic minorities and the urban and rural poor. No other scientific area so thoroughly transcends so many diverse areas of science and involves all of the NIH Institutes and Centers (ICs).

The NCMHD plays a key role in framing the NIH health disparities research agenda by conducting and supporting basic, clinical, social sciences, and behavioral health disparities research; developing research infrastructure and training programs; reaching out to and disseminating health information to minority and other health disparity populations; stimulating scientific programs within the NIH ICs to uncover the causes of health disparities and eliminate their impact on society; and developing and updating the NIH Health Disparities Strategic Plan.

This past year, the NCMHD, in collaboration with the NIH Director, every NIH IC, and the National Advisory Council on Minority Health and Health Disparities, completed the first comprehensive NIH Health Disparities Strategic Plan, based on scientific priorities and opportunities that will lead to new therapies and prevention strategies that will ultimately eliminate health disparities in America. This evolving plan will guide future NIH health disparities research efforts.

INNOVATIVE EFFORTS TO COMBAT HEALTH DISPARITIES

The NCMHD has accomplished much since its creation. Today, the NCMHD has 60 Health Disparities Centers of Excellence spread across the nation. These Centers of Excellence, now located in 23 states, the District of Columbia, and Puerto Rico,

support health disparities research, research training, and community involvement to identify factors that contribute to health disparities and to develop and implement new diagnostic, treatment, and prevention strategies.

The NCMHD addresses the national need to develop a diverse, strong, and a culturally competent scientific workforce by eliminating barriers that prevent racial and ethnic minority students and students from disadvantaged backgrounds from pursuing research careers. Currently, the NCMHD supports about 300 researchers from 38 states through its two Loan Repayment Programs, which help to level the playing field and make it possible for under represented individuals to enter the scientific, technological, and engineering workforce. These "Health Disparities Ambassadors" are key to creating the culturally competent health disparities and clinical research workforce of the future.

The NCMHD has also created a one-of-a-kind Research Endowment Program. Unique at the NIH, this program addresses the national need to build research and training capacity in institutions that make significant investments in the education and training of minority and disadvantaged individuals. This program is making it possible for 13 institutions located in 11 states and Puerto Rico to establish health disparities endowed chairs and programs, enhance student recruitment efforts, provide merit-based scholarships, recruit and retain faculty, develop innovative instruction delivery systems in minority and health disparities research areas, and access emerging technologies.

The NCMHD Research Infrastructure in Minority Institutions Program, born out of a partnership between the National Center of Research Resources and the Office of Research on Minority Health, (the predecessor to the NCMHD) is making it possible for institutions to target research efforts on health disparities that exist in the Southwest Border States; in rural communities, such as the Appalachia Region, the Mississippi Delta, and the Frontier States; and in urban centers of the nation. Currently, 11 institutions in eight states benefit from this program.

In addition to using its core programs, the NCMHD strategy to eliminate health disparities also includes leveraging NIH dollars and expertise by creating partnerships with the NIH ICs and other agencies within the Department of Health and Human Services to fund health disparities research, training, and outreach programs. Over the past two years alone, the NCMHD forged many new partnerships, supporting more than 400 research projects to combat health disparities in our nation.

CLOSING THE HEALTH DISPARITY GAP

Racial and ethnic minorities and other health disparity populations experience a disproportionate burden of illness, disability, and premature death due to cancer, cardiovascular disease and stroke, diabetes, HIV/AIDS, infectious diseases, infant mortality, and other diseases. The Department of Health and Human Services, through its "Closing the Gap Initiative," designates these areas as major research priorities. NCMHD programs focus on these priorities and many others. The following initiatives represent a small sampling of the richness and diversity of NCMHD activities.

Cancer

Cancer deaths vary by gender, race, and ethnicity. Certain racial and ethnic groups have lower survival rates than whites for most cancers. Colorectal cancer rates among Alaska Natives are higher than the national average and Asian Americans suffer disproportionately from stomach and liver cancers. African American men have the highest rates of colon, rectum, prostate, and lung cancers (*Healthy People 2010*).

NCMHD Health Disparities Centers of Excellence in 12 states across the nation are bringing to bear their state-of-the-art research and outreach programs to eliminate the impact of cancer on diverse populations. These efforts take place in Alabama, Arizona, California, Colorado, Georgia, Maryland, Mississippi, New York, Pennsylvania, Tennessee, Texas, and Virginia. One example of this intense effort is the American Indian and Alaska Native Health Disparities Center in Colorado, which conducts cancer research to address the needs of Native American and Alaska Native populations.

The NCMHD Research Infrastructure in Minority Institutions program, which focuses on building research capacity at minority serving institutions, also addresses cancer health disparities. The Charles R. Drew University is working to improve the detection and characterization of brain tumors, and researchers at San Francisco University are examining the impact of social support, spirituality, and depression on quality of life among breast cancer survivors from diverse populations.

Forty-five Health Disparities Ambassadors supported by our Loan Repayment programs have also set their sights on combating cancer health disparities in 17 states including Alabama, California, Colorado, Georgia, Illinois, Kansas, Massachusetts, Maryland, Michigan, Minnesota, North Carolina, New York, Pennsylvania, Tennessee, Texas, Virginia, Wisconsin, and in the District of Columbia. Some of the exciting work taking place under this program includes a community-based health promotion project to prevent cervical cancer in Vietnamese-American women; research studies on racial differences and barriers in obtaining breast, cervical, and colon cancer screening; and a population-based study that examines the variation in outcomes of colorectal cancer between African Americans and whites.

Collaboration with the other NIH Institutes and Centers has allowed the NCMHD to extend the reach of its scientific expertise to tackle cancer health disparities in rural populations. For example, the Appalachia Cancer Network, cosponsored by the NCMHD and the National Cancer Institute, addresses cancer in rural and medically underserved Appalachian populations in West Virginia, Kentucky, Tennessee, Virginia, Ohio, Pennsylvania, Maryland, and New York. The goal of this network is to reduce cancer incidence and mortality and to prevent future increases; to increase cancer survival; and to stimulate greater coordination and participation among regional, state, and community cancer control networks throughout Appalachia.

Cardiovascular Disease & Stroke

Cardiovascular disease takes a heavy toll on certain populations. Heart disease rates have been consistently higher in the African American population than in whites (*Healthy People 2010*). Data on stroke risk factors are sparse for most racial and ethnic populations, except for African Americans whose stroke deaths, when adjusted for age, are almost 80 percent higher than in whites (*Healthy People 2010*).

Today, 13 NCMHD Health Disparities Centers of Excellence, located in nine states across the nation including California, Georgia, Hawaii, Maryland, Mississippi, North Carolina, New York, Pennsylvania, and Texas focus on eliminating disparities due to cardiovascular disease. Three Health Disparities Centers of Excellence in Georgia, Mississippi, and New York focus on stroke research. The NCMHD also supports 20 Health Disparities Ambassadors spread across 11 states, including California, Florida, Illinois, Indiana, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Ohio, and Texas, who have set their sights on eliminating health disparities due to cardiovascular disease.

The NCMHD Health Disparities Center of Excellence at Jackson State University in Jackson, Mississippi is built on a partnership with the University of Mississippi Medical Center, the University of Pittsburgh, and the Jackson Medical Mall Foundation. This Center's research agenda focuses on cardiovascular disease, stroke, and cancer in the African American population in Mississippi.

The NCMHD also partners with its fellow NIH ICs, in the battle against cardiovascular disease and stroke disparities. The NCMHD partners with the National Heart, Lung, and Blood Institute to support the Jackson Heart Study. This study evaluates the environmental and genetic factors contributing to the disproportionate incidence of cardiovascular disease in African American men and women living in Mississippi. To date, almost 5,000 participants have benefitted from the program by visiting the clinic, with an average of 25 participants per week.

The NCMHD and the National Institute of Neurological Disorders and Stroke partner to support two Specialized Neuroscience Research Programs at the Morehouse School of Medicine and at the University of Texas at San Antonio. This funding allows institutions to develop state-of-the-art neuroscience research programs; strengthen collaborations and resource-sharing between minority medical and graduate schools, community-based organizations, and leading neuroscience laboratories; expand training opportunities for minority students to access and prepare for careers in neuroscience research; and build new stroke research capacity.

Diabetes

Certain communities, including Hispanics, American Indians, African Americans, and certain Pacific Islanders and Asian populations, as well as economically disadvantaged and older people suffer disproportionately from diabetes (*Healthy People 2010*). Diabetes is the target of 27 Health Disparities Centers of Excellence in 17 states including Alabama, Arizona, California, Colorado, Georgia, Hawaii, Illinois, New York, North Carolina, North Dakota, Maryland, Mississippi, Oklahoma, Pennsylvania, South Carolina, Texas, and Wisconsin, as well as the District of Columbia. These programs include the University of Hawaii at Manoa, where efforts are underway to reduce and eliminate the major complications of diabetes in Pacific Islanders. The University of Pennsylvania is developing behavioral strategies for re-

ducing obesity, a major factor contributing to diabetes in Latino and African American communities.

The NCMHD has also deployed 15 Health Disparities Ambassadors to 10 states, including Alabama, California, Florida, Georgia, Illinois, Massachusetts, New Hampshire, New York, Texas, and Virginia in the effort to eliminate diabetes-related health disparities. These individuals are conducting several important projects including reducing obesity in diabetic African American women in the state of Georgia and conducting educational interventions to prevent type 2 diabetes in middle school children in Alabama. Under the NCMHD Research Endowment program, Xavier University of Louisiana is increasing the diabetes research capability of its College of Pharmacy, promoting health disparities research, and increasing the pool of well educated under represented minorities who pursue advanced education in biomedical and behavioral research.

New NCMHD partnerships are also playing a significant role in eliminating diabetes health disparities. The NCMHD and the Indian Health Service recently formed a partnership to develop the Tribal Epidemiology Centers Program to address and eliminate health disparities, including diabetes disparities, experienced by American Indians and Alaska Natives. Recent NCMHD support enabled the creation of a new Northern Plains Tribal Epidemiology Center in Rapid City, South Dakota, continued funding for the other six existing EpiCenters, and the development of a summer training institute for Indian Health professionals. The funding will assist the EpiCenters to carry out their training program for local health staff, and expand their outreach activities to include a community-based research training program.

HIV/AIDS

The disproportionate impact of HIV/AIDS on certain populations underscores the importance of sustained research and prevention efforts. In 2002, the AIDS diagnosis rate among African Americans was almost 11 times the rate among whites. African American women had a 23-times greater diagnosis rate than white women. African American men had almost a nine-times greater rate of AIDS diagnosis than white men. (Centers for Disease Control and Prevention Division of HIV/AIDS Prevention 2003). In 2000, the AIDS incidence among Hispanics was 22.5 per 100,000 population, more then three times the rate for whites (Centers for Disease Control and Prevention Division of HIV/AIDS Prevention 2002:1).

In its fight against HIV/AIDS health disparities, the NCMHD partners with the Centers for Disease Control and Prevention to support the Racial and Ethnic Approaches to Community Health (REACH) Program. REACH serves African American, Asian American, Pacific Islander, Hispanic American, American Indian, and Alaskan Native populations at increased risk for HIV/AIDS, cardiovascular disease, breast and cervical cancer, diabetes and infant mortality. REACH develops, implements, and evaluates innovative community level intervention demonstrations that could be effective in eliminating health disparities by 2010.

With the Agency for Healthcare Research and Quality, the NCMHD supports the EXCEED Program to examine the underlying causes and contributing factors for racial and ethnic disparities in health care and to identify and implement strategies for reducing and eliminating those disparities. Under this initiative, the Medical University of South Carolina is examining strategies to address HIV/AIDS disparities in health status between African Americans and whites, and the Baylor College of Medicine is assessing the extent to which problems in doctor-patient communication contribute to racial and ethnic disparities in health care use.

Infant Mortality

In recent years, infant mortality rates in the United States have steadily declined; yet the rate of Sudden Infant Death Syndrome among African Americans is still twice that of whites. African American women continue to be three to four times more likely than white women to die of pregnancy-related complications. Hispanic women are less likely than whites to enter into early prenatal care. Fetal Alcohol Syndrome disproportionately impacts American Indian, Alaska Native, and African American babies. (*Healthy People 2010*).

The NCMHD has Health Disparities Centers of Excellence in six states including Alabama, Florida, Georgia, Texas, Iowa, and Wisconsin that focus their efforts to improve the health of mothers and their infants. One of these, the "Mexican-American Women's Health Project Center" at the University of Texas, El Paso, partners with established Hispanic health disparities researchers at the University of Arizona. Their research efforts focus on modifying behaviors of Mexican-American women relating to alcohol use; maternal health and nutrition; smoking cessation; and the pursuit of recommended Pap and HPV screening tests. Another Center at

the University of Northern Iowa focuses on maternal and child health disparities to address the special health needs of Iowa's minority groups, which include urban African Americans, members of the Meskwaki Indian Tribe, rural families, growing populations of Latino and East African immigrants, and refugees from Bosnia and the former Soviet Union.

The NCMHD also supports six Health Disparities Ambassadors through its Loan Repayment Programs, who are focusing their attention on infant mortality health disparities. These efforts is take place in Florida, Maryland, Michigan, Missouri, North Carolina, and Pennsylvania. Ongoing efforts include evaluating the link between sexually transmitted diseases and infant mortality; determining leading health indicators for women and girls; and creating logic models for maternal, child, and family health programs.

RURAL HEALTH

Another top priority of the NCMHD is improving rural health across the nation. In pursuit of this goal, the NCMHD established an innovative Health Disparities Center of Excellence partnership between Clemson University and Voorhees College, a Historically Black Institution in South Carolina. This partnership will build capacity for research, training, and outreach to address health disparities in rural Hispanic and African American communities in South Carolina. The Tuskegee University and the University of Alabama, Tuscaloosa Health Disparities Center of Excellence partnership, in conjunction with the University of Alabama Institute for Rural Health Research and community organizations, focuses on adult immunization, infant mortality, cancer, and diabetes.

Over the past year, the NCMHD also created opportunities to include the expertise of other NIH ICs in addressing the needs of rural communities, forming 16 new rural health partnerships with the NCI, NHLBI, NIAAA, NIDA, NIEHS, NIMH, and the NINR. Examples of these new projects include the Appalachia Cancer Network; the Deep South Network for Cancer Control; the Rural Caregiver Telehealth Intervention Trial; and studies on the effects of alcohol and violence on rural women; coronary artery disease in Alaska Natives; migrant worker health and the environment; mental health treatment for rural Mexican Americans, African Americans, women, and the poor; cardiovascular health training and outreach in Latino communities; and substance abuse among Ojibwe children and youth.

CONCLUSION

The diversity of the American population is one of the greatest assets of the nation. One of the greatest challenges facing the nation is reducing and eliminating the profound disparity in health status that exists for many of its populations. Without decisive action now, the health challenges of the 21st century will expand along with the increasing number of racial and ethnic minorities, inhabitants of rural areas, and low socioeconomic populations.

The NCMHD will continue to combat health disparities through our flagship programs. We will explore new opportunities to support academic development for the health disparity researchers of tomorrow. We will seek to create innovative programs to serve as a bridge between NCMHD capacity building programs and an investigator's first independent research effort. Cognizant of the value of engaging communities in the elimination of health disparities, we will lead efforts to conduct effective community-based outreach and research to our numerous constituents. We will continue our legacy of creating and nurturing partnerships to further increase the reach of our activities to eliminate health disparities and we will encourage our fellow NIH ICs to join the core health disparities programs of the NCMHD. The NIH Roadmap Initiative should also provide opportunities for the NCMHD constituent populations and research community to participate in interdisciplinary research, clinical research, and technology.

Our vision of the future is a collective one that is embodied in the NIH Health Disparities Strategic Plan. With leadership, commitment, and strong scientific partnerships the NIH can advance scientific discovery to ensure the health of all Americans. Working together, we can turn the vision of an America where all citizens have an equal opportunity to live long, healthy, and productive lives into reality.

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 2005, a sum of $1,094,141,000, including support for AIDS research,

which reflects a net decrease of $84,815,000 over the comparable fiscal year 2004 appropriation, due entirely to the phasing out of extramural construction projects for fiscal year 2005.

It is a pleasure once again to have the opportunity to present the accomplishments of NCRR-supported investigators and the future directions for NCRR programs. As a component of the National Institutes of Health, NCRR enables all lines of health-related discovery by supporting the creation and development of critical research resources and technologies. Because significant discoveries can be made at a variety of levels—from molecules to patients, or even patient populations NCRR supports a wide range of research resources across several disciplines. These resources include state-of-the-art clinical research environments, such as the nationwide network of General Clinical Research Centers. The GCRCs facilitate clinical research and protect the safety of participants in research. Each year more than 10,500 NIH-supported investigators conduct nearly 8,000 research projects at the GCRCs, predominantly through more than a half million outpatient research visits.

NCRR also supports research resources that develop and enhance scientific access to advanced technologies, nonhuman models for the study of human diseases, and career development and training. Because of its trans-NIH focus, NCRR is well-positioned to facilitate research by promoting the sharing of research tools and technologies as well as providing the tools for research collaborations so that research teams may address more complex research problems.

TECHNOLOGY AND INSTRUMENTATION

NCRR strives to ensure that neither the lack of research resources nor technology development becomes rate-limiting for research. Two Nobel Prize winners in 2003 can vouch for the importance of having ready access to NCRR-supported resources. Dr. Roderick MacKinnon of Rockefeller University, co-recipient of the Nobel Prize in Chemistry, was honored for his groundbreaking studies of the structures and functions of ion channels, which control the movement of electrically charged atoms across cell membranes. Ion channel malfunctions can trigger a host of human disorders, including irregular heart rhythms and seizure disorders. Dr. MacKinnon noted that his award-winning discoveries depended on having access to the scientific expertise and advanced research instrumentation available at NCRR-supported resources that specialize in mass spectrometry and crystallography of complex molecules.

The challenge for NCRR is to keep pace with the biomedical community's changing needs for research tools and to ensure that tomorrow's research queries have tomorrow's critical instrumentation and technologies in hand. The research resources and tools needed for scientific investigations change dramatically over time as more complex research queries are posed and require new technologies. Many research tools now considered critical to understanding the cause of disease and protecting the health of Americans were unheard of just a few years ago. For instance, the Magnetic Resonance Imagers, or MRIs, now found in hospitals and medical centers across the country were rare and experimental less than 20 years ago. Dr. Paul Lauterbur of the University of Illinois, Urbana-Champaign, depended on NCRR for many of his investigations into magnetic resonance imaging. Dr. Lauterbur was corecipient of the Nobel Prize in Physiology or Medicine for his studies that led to the development of MRI. From 1990 to 2000, Dr. Lauterbur headed an NCRR-funded magnetic resonance research center, which helped to facilitate the evolution of MRI into the invaluable diagnostic and clinical research tool that it is today.

CLINICAL RESEARCH RESOURCES

Just as NCRR technology and instrumentation resources laid the foundation for critical discovery in the basic and applied sciences, NCRR also catalyzes clinical and patient-oriented research through the network of GCRCs. In addition, NCRR develops and supplies investigators with clinical-grade biomaterials, such as vectors for gene therapy and human pancreatic islets for transplantation into patients with type 1 diabetes.

Research on rare diseases is one area where the GCRCs are ideally positioned to catalyze clinical research. Rare disease research is challenging in part because few patients with a particular rare disease can be recruited from any one clinical center. The nationally distributed network of the GCRCs makes them well-suited for enabling multicenter studies of rare conditions. Therefore, NCRR has partnered with the NIH Office of Rare Diseases and other groups to launch a network of Rare Diseases Clinical Research Centers. The network provides researchers with access to sufficient numbers of affected patients for statistically meaningful studies. The net-

work also facilitates collaborations among scientists from multiple disciplines and institutions.

To ensure the safety of human subjects participating in clinical research projects, clinical investigators must adhere to Federal, state and local regulations, policies, and guidelines. Yet these necessary responsibilities place heavy demands on the time of already-busy clinician investigators. To address this issue, NCRR established a new GCRC staff position known as the Research Subject Advocate (RSA). The RSA assists GCRC investigators, nurses, and staff to underscore the safe and ethical conduct of clinical studies and represents the interests of research participants. NCRR plans to extend and strengthen the role of RSA in an approach that complements that undertaken by the host institution.

HEALTH DISPARITIES

NCRR also supports clinical research studies on health disparities, or diseases that disproportionately affect racial and ethnic minority populations. NCRR has joined with the National Institute of Mental Health to establish three Comprehensive Centers on Health Disparities. These Centers will further develop the capacity of Research Centers in Minority Institutions' (RCMI) medical schools to conduct basic and clinical research in type 2 diabetes and cardiovascular disease, both of which disproportionately affect minority populations. The Centers will provide support to further develop the requisite research infrastructure, recruit magnet clinical investigators, recruit and develop promising junior faculty, and facilitate substantial collaboration between the RCMI grantee institutions and more research-intensive universities. NCRR also supports a Stroke Prevention and Intervention Research Program that focuses on minorities, as well as a mentored clinical research career development program to provide clinical research training for doctoral and postdoctoral candidates in minority institutions.

BIOINFORMATICS AND COMPUTER NETWORKS

Whether studying clinical manifestations of disease or the basic biology of cells and tissues, today's biomedical researchers generate vast data sets. This data deluge has increased scientific demand for access to scaleable computation and modern management tools. A related and equally important trend is the fact that biomedical research projects are becoming broader in scope. For example, neuroscientists now want to correlate brain images with events at cellular and molecular levels, including gene expression. These broad research projects require large multidisciplinary teams, gathered from scientists distributed across the country.

To meet the challenges associated with these trends, NCRR supports the development of bioinformatics tools, including the software programs or algorithms that help scientists manage and analyze their data. NCRR also is instrumental in the creation of high-performance computer networks that link laboratories throughout the United States. A few years ago, NCRR joined with the National Science Foundation, Internet2, and investigators from several universities to establish the Biomedical Informatics Research Network (BIRN). The BIRN provides the tools for researchers to pool their data and to use federated databases so that they can oversee the integrity of their data, use bioinformatics tools for data mining, and visualize their data. In fiscal year 2004, NCRR began expanding the number of BIRN sites in order to establish a national infrastructure of bioinformatics tools and provide access to scaleable computing that, in turn, is linked to a nationally distributed network of modern imaging capabilities for studies of degenerative brain disorders.

Other components of the BIRN network will link underserved institutions, such as doctoral degree-granting minority institutions and institutions in states that have received limited NIH research funding because they include very few research trained investigators, otherwise known as Institutional Development Award (IDeA) states. The networks will foster collaborative research and help investigators create a virtual critical mass of investigators. The BIRN also will foster collaborations across institutions located at remote sites. NCRR plans to establish a network for institutions with medical schools that are associated with NCRR's Research Centers in Minority Institutions (RCMI) Program. This electronic network will facilitate their participation in large clinical trials and other research studies and help define the factors contributing to health disparities among minority populations and ways to overcome those factors.

In concert with other NIH components, NCRR participates in many NIH Roadmap initiatives for example, development of a National Electronic Clinical Trials and Research (NECTAR) network, which will form the backbone for all clinical research networks. An important component of NECTAR will be the standardization of patient data collection and storage procedures, which will facilitate data sharing

by investigators. NCRR also supports other trans NIH Roadmap initiatives, including the National Centers for Biomedical Computing, Exploratory Centers for Interdisciplinary Research, and National Technology Centers for Networks and Pathways.

PROTEOMICS

The availability of complete genomes for a variety of organisms provides an important first step in understanding many complicated biological questions, including the molecular basis for disease. The next step in this process will be to develop technologies to quantitate spatiotemporal differences in the levels of gene expression, assess post-translational modifications of proteins, and characterize protein-protein interactions in both healthy and diseased cells.

NCRR will support the development of the necessary technology and infrastructure to advance the science of proteomics. An advanced proteomics center will focus on multiple technologies, including techniques for protein purification, structural techniques, mass spectrometry, and DNA microarray instrumentation along with the necessary bioinformatics.

CONCLUSION

I have today noted two important trends in biomedical research the rapid accumulation of data and the broadening scope of research studies. To these, I must add a third trend namely, the increasingly collaborative nature of biomedical science. Some of today's most pressing questions in biomedical science are so complex, so multifaceted, that they cannot be addressed by a single investigator or even a single research laboratory. In many cases, teams of scientists with diverse skills and backgrounds are needed to get the job done.

It is my belief that this emphasis on interdisciplinary collaborations, as evidenced by the multiple NIH Roadmap initiatives related to this area, will bring about unprecedented gains in biomedical science, and ultimately lead to improved health of all U.S. citizens. Finally, as the research paradigm evolves toward greater complexity, the infrastructure required to support that research must evolve too.

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 2005 President's budget request for the National Institute of Child Health and Human Development (NICHD). The fiscal year 2005 budget includes $1,280.9 million, an increase of $39.1 million over the comparable fiscal year 2004 appropriation of $1,241.8 million.

The NIH Roadmap provides the schema to guide the NICHD in achieving its programmatic and research goals.

Today I would like to share with you how the research supported by this committee is improving the lives of children, mothers, adults and families, and helping to reduce health disparities. The NICHD is participating in the trans-NIH obesity initiative identifying how primary care physicians can help children maintain a healthy weight.

ENCOURAGING HEALTHY BIRTH OUTCOMES

Preeclampsia is a condition that affects five out of every hundred women who become pregnant. Preeclampsia can occur suddenly, and without warning, causing women to develop dangerously high blood pressure. In some cases, the condition may progress to eclampsia in which women experience potentially fatal seizures. Infants born to mothers with preeclampsia may be extremely small for their age or may be born prematurely, putting them at risk for a variety of other birth complications. Although a woman's high blood pressure and seizures can be treated, the only cure for preeclampsia is delivery of the baby. In a significant step toward treating preeclampsia, researchers have identified substances in the blood that have the potential to predict who will develop preeclampsia. This knowledge may help us treat women before preeclampsia becomes a serious problem, for them and their infant.

We have also intensified our research in the area of stillbirth, a devastating occurrence that affects far too many families. Health care providers use the term stillbirth to describe the loss of a fetus after the 20th week of pregnancy. Stillbirth can occur before delivery or as a result of complications during labor and delivery. In at least half of all cases, researchers can find no cause for the pregnancy loss. We hope to change that. The NICHD has established the Stillbirth Collaborative Net-

work, which consists of research centers in Texas, Utah, Rhode Island, and Georgia. In each center, a team of specialists, including obstetricians, nurses, statisticians, and even grief counselors will seek to understand the causes of stillbirth and eventually find ways to prevent these deaths.

One way to increase the chances of a healthy pregnancy and healthy birth outcome is to avoid alcohol during pregnancy. Infants born to mothers who drink heavily during pregnancy are known to be at risk for mental retardation and birth defects. They are also at increased risk for Sudden Infant Death Syndrome (SIDS). NICHD researchers have now identified another reason that women should not consume alcohol during pregnancy: exposure to alcohol before birth affects the developing nervous system in the arms and legs.

Recently, scientists in NICHD's Maternal-Fetal Medicine Units Network reported a breakthrough in reducing a major cause of infant mortality and the subsequent long term health problems associated with prematurity. The scientists, working collaboratively in 14 academic health centers across the United States, demonstrated that progesterone administered to women at risk for premature birth could significantly reduce the likelihood of early delivery. This was a very significant discovery and we were delighted that others recognized its importance. A few weeks ago, Parade magazine identified this discovery as one of the ten most significant health advances of the past year.

NEW FRAGILE X CENTERS TO DEVELOP TREATMENT OPTIONS

In 2003, the NICHD funded three new Fragile X research centers. Teams of researchers at each of the centers located in North Carolina, Texas, and Washington state are developing new ways to diagnose both the mild and severe forms of the condition, as well as new treatments. Fragile X syndrome is the most common genetically-inherited form of mental retardation currently known. It occurs in 1 out of every 2,000 males and in 1 in 4,000 females. The syndrome is caused by a mutation in a specific gene, known as FMR1, on the X chromosome. In its fully-mutated form, the FMR1 gene interferes with normal development, resulting in mental retardation. In a partially mutated form, the FMR1 gene can cause fragile X syndrome in the children of a parent who is a carrier. Until recently, it was thought that carriers did not have any symptoms. Researchers have learned that some people with a form of fragile X have mild cognitive and emotional problems. In addition, some female carriers are likely to undergo premature menopause. In older male carriers, the fragile X is associated with a neurological degenerative syndrome. Identifying a means to predict which carriers will develop the symptoms could be a first step toward developing new treatments for these often overlooked symptoms. The Fragile X Research Centers are focusing their research on how the fragile X affects the developing brain and nervous system, how the disorder progresses throughout an individual's life span, and treatments that can improve the behavior and mental functioning of people with fragile X syndrome.

IMPROVING TREATMENT FOR CRITICALLY ILL CHILDREN

Critical care medicine for children is an emerging field where, in general, physicians continue to rely upon adult treatments that have not yet been tested for effectiveness in a young population. To change this situation, the NICHD will help establish a national pediatric critical care research network to develop and evaluate treatments for children with disabling conditions. The initiative will foster collaborations among scientists in many different fields and will support research such as the best approach to care for children with brain injury, the most effective way to transition a critically ill child from an acute care to a rehabilitation setting, and the care of critically ill children in the event of a bioterrorism attack.

CUTTING OBESITY THROUGH RESEARCH AND PROGRAMS

The increase in overweight and obesity among adults and children is a major public health concern. In fact, in a recent analysis of international data, NICHD researchers documented that U.S. teenagers were more overweight than youth in 14 other developed countries. Like many other health conditions that affect adults, the antecedents of adult obesity can be found in childhood. Young children who are overweight are likely to be overweight as adults. There is no single explanation for the increase in childhood overweight and there is no single solution. However, we know we must devise successful interventions that help children maintain a healthy weight. As part of the trans-NIH initiative, the NICHD will lead a major effort to determine whether a weight control program for children and youth led by primary care physicians as part of a comprehensive community-based effort can be successful. Currently, most weight management programs are administered through spe-

cialty clinics. However, there is strong evidence that an appropriate intervention by a physician can have a significant impact on personal behaviors such as tobacco use. Effective weight management programs in a primary care setting would be accessible to large numbers of children and would minimize the geographic, social, and economic barriers that commercial weight management programs can impose.

We are also developing an exciting research-based program that helps to teach young children the fundamentals of good nutrition and physical activity as well as how to make sense of the messages that appear in the media. Three years ago, this committee provided funds to the NICHD and other health agencies to develop programs that encourage young people to engage in healthy behaviors. In response to this directive, the NICHD has developed "Media Smart Youth," an after school program for children between nine and 13 years of age. The program focuses on good nutrition and physical activity. But it also provides skills to young children to interpret the messages about food and snacks they see on television, in magazines, and on the Internet. As part of their activity, the children who take part in Media Smart Youth develop messages about the importance of good nutrition and physical activity for their peers. The program has been tested with youth groups around the country. In fact, the children at P.S. 127 in the Bronx who took part in this program developed a message about physical activity for young people that appeared for 30 minutes on the Panasonic "jumbotron" screen in Times Square.

HELPING YOUNG CHILDREN PREPARE FOR SCHOOL

The preschool years are crucial for learning language, social skills, and developing the intellectual capabilities that set the stage for later success in school. Yet, comparatively little is known about how to help young children obtain the greatest benefit possible from the preschool experience. In December 2003, NICHD joined with two other HHS agencies and the Department of Education, and launched a five year research initiative to find the best ways to help preschoolers at risk for failure in school acquire the skills they need for school success. The initiative provided $7.4 million in funding for the first year. Eight projects were funded to test research-based approaches to preschool curricula, Internet based approaches to training preschool teachers, and the importance of parental involvement for preparing children to enter school. Funds requested for fiscal year 2005 will allow us to expand this effort by funding academic researchers and small businesses to develop and produce more effective measurements of outcomes from preschool interventions.

SIDS RESEARCH SUPPORTS PROGRAM OUTREACH

We have known for more than 10 years that placing infants on their backs to sleep reduces their risk of Sudden Infant Death Syndrome (SIDS). In fact, since the NICHD launched the Back to Sleep SIDS risk reduction campaign in 1994, the rate of SIDS in the United States has declined by more than 50 percent. The NICHD continues a vigorous research program to learn more about the causes and prevention of SIDS. For instance, a team of NICHD-funded researchers in Ohio recently discovered that infants who were placed to sleep on their backs were less likely to develop fevers, get stuffy noses or develop ear infection. Ear infections alone cost the health care system an estimated $5 billion a year. So this simple behavior of placing infants on their backs to sleep not only saves lives, it can save the health care system large sums money by reducing the use of antibiotics to treat ear infections. We also learned that infants who are normally placed to sleep on their backs are at greatly increased risk of SIDS when they are occasionally placed to sleep on their stomachs. New research on SIDS continues to shape our SIDS risk reduction outreach campaign. More recently, a major focus of the campaign has been reducing the risks of SIDS in African American communities.

SIDS rates for African American babies have declined significantly since the NICHD initiated its Back to Sleep campaign ten years ago. Yet, the SIDS rate for African American infants is more than twice that of white infants. To address this health disparity, the NICHD joined forces with three national African American organizations in a unique collaboration to reduce the risks of SIDS in African American communities. The Alpha Kappa Alpha Sorority, the National Coalition of 100 Black Women, and the Women in the NAACP, sponsored three regional summit meetings to raise SIDS awareness and train community leaders to be resources and spokespersons for SIDS risk reduction in their communities. The summit meetings were held in Tuskegee Alabama, Detroit Michigan, and Los Angeles California, and they helped build an infrastructure to involve faith-based, community, and service organizations in reducing the risks of SIDS and in promoting the health of infants. In Detroit, for instance, the summit ended with a "SIDS Sunday," which was held at Hartford Memorial Baptist Church on the Sunday following that summit. After-

wards, other churches across the region held a "SIDS Sunday," where pastors shared SIDS information from their pulpits, in their church bulletins, and with nurses and care givers in their childcare centers and nurseries. The successful collaboration of researchers, government officials, and the community will create a strong foundation for launching other interventions to eliminate health disparities.

MOTHERS LEAVING WELFARE HAD NO EFFECT ON PRESCHOOLERS

A study that received much of its funding from the NICHD demonstrated that when a mother leaves welfare to enter the labor force, it does not seem to have any negative effects on preschoolers or young adolescents. The study was undertaken in response to the Personal Responsibility and Work Opportunity Reconciliation Act of 1996, which mandated stricter welfare requirements for all welfare recipients. The researchers theorize that the positive and negative effects of going off welfare and getting a job may cancel each other out. For example, the increase in family income that comes with leaving welfare thought to relieve the stress on a family may make up for the decreased amount of time that mothers spend with their young children. In addition, mother's transition to work had a slightly positive effect on teens, reducing the teens' levels of anxiety. Conversely, teens whose mothers left the job market and went on welfare developed increased anxiety levels.

MICROBICIDES THAT CAN PREVENT SEXUALLY TRANSMITTED INFECTIONS

The NICHD is funding a number of projects to develop microbicidal compounds to prevent the spread of sexually transmitted infections and HIV. These compounds not only have the potential to prevent the spread of disease-causing bacteria and viruses, but may also be effective in preventing pregnancy. One project is a large scale test of the contraceptive effectiveness of Buffergel, a compound that kills the microorganisms that cause sexually transmitted diseases, and shows promise as a contraceptive. Another project is studying a microbicidal spermicide, C31G. The compound's effectiveness will be compared to that of a conventional spermicide preparation. Working with the National Institute of Allergy and Infectious Diseases, the NICHD has funded a new system to test the quality of potential microbicides to determine if they warrant further testing in human beings.

SAFER DRUGS FOR USE WITH CHILDREN

In January 2002, President Bush signed into law the Best Pharmaceuticals for Children Act (BPCA). The law recognizes that drugs may have different effects in children than they do in adults, and seeks testing for drugs given to children. For roughly 75 percent of the drugs approved by the U.S. Food and Drug Administration (FDA) for adults, there is inadequate information available to ensure the safety and effectiveness of the drugs in children. Moreover, there is little or no data to guide physicians in prescribing dosages of these drugs for children. Working in close collaboration, the NICHD and the FDA, as directed by the BPCA, identified several high priority drugs to be tested. The NICHD is currently establishing partnerships with pediatric drug study networks in other NIH Institutes to expedite the study of other clinically important drugs.

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 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.

NATIONAL CHILDREN'S STUDY

In a few short years, The National Children's Study has evolved from a concept to an exciting research collaboration poised to answer critical questions about child development. The fiscal year 2005 budget request continues planning dollars for this important project, but does not reflect funding to launch the study itself, since it is still being developed. The National Children's Study plans to examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. The NICHD serves as the lead agency on this ambitious project, working closely with the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, and the U.S. Environmental Protection Agency. The

collaboration involves government agencies, the research community, industry, and community groups.

NIH ROADMAP AND CLINICAL RESEARCH

To ensure that the necessary clinical research workforce is available to translate laboratory findings to improved treatments for patients, the NIH Roadmap is strengthening several stages in the career path for these researchers. One new program will provide clinical research experience and didactic training during medical and dental school. Another will train doctorate-level professionals in multi disciplinary collaborative clinical research settings that reflect the diversity of today's clinical research team. To attract community practitioners to clinical research, the NIH plans to create a cadre of National Clinical Research Associates, community practitioners trained in clinical research who will refer patients to large clinical trials to enhance patient recruitment and more rapidly test potential therapies. The NIH is also identifying ways to improve peer review of clinical research grant applications and to enhance promotion and tenure policies in academia for clinical researchers.

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 2005, a sum of $1,876,196,000, which includes $150 million for the Special Appropriation for Research on Type 1 Diabetes through Sec. 330B of the Public Health Service Act. The NIDDK transfers some of these funds to other institutes of the NIH and to the Centers for Disease Control and Prevention (CDC). Adjusted for mandatory funds, this is an increase of $54,956,000 over the fiscal year 2004 enacted level of $1,821,240,000 comparable for transfers proposed in the President's request.

HIGHLIGHTS OF PROGRAM ENHANCEMENTS

I appreciate the opportunity to testify on behalf of the NIDDK's efforts to combat the wide range of debilitating, chronic health problems within our research mission, many of which are caused directly or indirectly by obesity. Last year, I reported the creation of an NIDDK Office of Obesity Research to intensify the fight against this major public health problem, which is harmful both in its own right and as a driver of type 2 diabetes, especially in minorities and the young. Obesity can also be a contributing factor to nonalcoholic fatty liver disease, gallstones, end-stage kidney disease, and urinary incontinence. According to the CDC, approximately 64 percent of adults and 15 percent of children and teens are considered either overweight or obese. Disturbingly, these rates reflect skyrocketing trends over the past two decades. To accelerate research to combat this epidemic, the NIH Director established the NIH Obesity Research Task Force in April 2003, with co-chairmanship by the Directors of the NIDDK and the National Heart, Lung, and Blood Institute (NHLBI). I am pleased to report that the Task Force has completed a draft Strategic Plan for NIH Obesity Research, with input from external scientific and lay experts. This Plan is posted on a newly established Web site that will alert investigators to NIH obesity research funding opportunities, and also inform the public about NIH efforts. Both the Plan and the Web site are dynamic, and will evolve with changes in science and public health needs. Acting alone, the NIH cannot halt or reverse obesity; however, by generating and disseminating new research knowledge, we can lend a vital scientific dimension to what must truly be a multifaceted national effort.

The Strategic Plan will contribute to the prevention and treatment of obesity by bolstering research in three major avenues: (1) behavioral and environmental approaches to modify lifestyle; (2) pharmacologic, surgical, or other biological/medical approaches; and (3) ways to break the link between obesity and its associated health conditions, known as co-morbidities. Within the goals and strategies outlined in the Plan, the NIDDK will have a major role in three trans-NIH initiatives.

The first is an effort to combat pediatric obesity in site-specific ways—both in primary-care settings, and in other community settings, such as the home, day-care, pre-school, school, and other venues. Researchers will explore effective methods for the primary prevention of inappropriate weight gain among children and adolescents who are not overweight; secondary approaches to prevent further weight gain among those already overweight or obese; and tertiary efforts to prevent co-morbidities. We will build on studies the NIDDK is already pursuing to evaluate the effects of so-called "natural experiments" in which States or localities are chang-

ing the food and lifestyle choices and cues that students encounter in school settings. We will also build on studies to determine the effects of modifying the home environment, such as the influence of T.V.-watching on obesity, eating behavior, and physical activity. Our children are precious, and we should do all we can to spare them the serious health problems that can attend a lifelong struggle with obesity.

A second trans-NIH initiative will focus on the neurobiological basis of obesity, which includes the intricate brain-gut circuits that signal hunger and fullness, and thus are crucial to maintaining the body's energy balance between calories consumed as food and expended in physical activity. I previously reported on several hormones that mediate energy-related signals, such as leptin, adiponectin, and ghrelin. By exploiting these and other findings through innovative collaborations between biomedical and behavioral researchers, we will delineate the many pathways that modulate the control of eating behavior in humans.

In a third trans-NIH initiative, the NIDDK will take the leadership role in creation of an Intramural Obesity Clinical Research Program to capitalize on the unique, collaborative infrastructure of the NIH Clinical Research Center. This Program will foster multidisciplinary approaches to obesity research in areas such as metabolism, endocrinology, nutrition, cardiovascular biology, liver and other digestive diseases, genetics, and the behavioral sciences. A "magnet" approach will draw upon the extensive expertise and resources of the NIH intramural program to frame state-of-the-art clinical investigative strategies and harness emerging technologies.

In addition to these trans-NIH initiatives, the NIDDK will support a range of research, including ancillary studies to maximize the resources already invested in ongoing clinical trials. We will pursue challenging questions about obesity. What factors control where fat is deposited, and the relationship between its location and differences in metabolism, fat-cell regeneration, cell signaling, and associated comorbidities of obesity? What is the relationship between obesity and abnormal levels of circulating and stored lipids, which are a hallmark of metabolic problems? Can we identify biomarkers of change brought on by the obese state? What genetic abnormalities underlie the co-morbidities of obesity? What steps can people take to achieve long-term maintenance of weight loss?

As obesity is escalating in the United States, so is type 2 diabetes. New estimates from the CDC place the number of people with diabetes at 18.2 million, and about 90–95 percent of them have this form of the disease. Disturbingly, about 5.2 million of those affected are unaware. Millions of adults also have a condition called "prediabetes," in which glucose levels are elevated, but not as high as in full-blown diabetes. Because clinical trials have demonstrated that lifestyle and medical interventions can significantly delay or prevent disease onset in those at high risk, it is critical to identify these individuals and underscore the preventive actions they can take. The NIDDK is taking vigorous steps to foster the generation of new laboratory tests to improve diabetes detection, as well as to promote the development of more cost-effective strategies to pinpoint those at risk who can benefit most from early intervention. We are also supporting studies to translate important advances from clinical trials in diabetes prevention and care into medical practice. For example, for a low-income Latino population, we are supporting a clinical trial to compare current translation efforts for type 2 diabetes prevention with a method that incorporates culturally-sensitive strategies. We are also studying an interactive video conferencing system to enable communication between health professionals at a large medical center and diabetes patients in a rural state, with limited access to health care providers. Interventions that are successful in these trials could pave the way to widespread use by communities throughout the country.

Once considered an "adult-onset" disease, type 2 diabetes is being increasingly diagnosed in children and adolescents, especially in minority populations. We are launching a multi-center, school-based trial (STOPP-T2D) to find ways to prevent the development of risk factors for type 2 diabetes in middle-school children. The trial will include school-based programs targeting nutrition, physical activity, and behavior modification. Another multicenter trial (Treatment Options for Type 2 Diabetes in Adolescents and Youth TODAY) will seek the best treatment strategies.

Diabetes can lead to serious complications, such as blindness, irreversible kidney failure, lower limb amputation, and heart disease. We have established an NIDDK Diabetes Complications Working Group, which is charged with seamless integration of these activities across the Institute. The NIDDK also recently convened an international group of clinical and basic researchers to brainstorm research approaches to the urologic complications of diabetes. Because complications can affect many organs, we collaborate with other components of NIH and the Department to benefit from their expertise. For example, studies have shown that the process of new blood vessel formation, called "angiogenesis"—traditionally studied in relation to cancer—is also critically important to vascular changes in diabetes, such as the dangerous

proliferation of blood vessels in the eye that can lead to blindness. Angiogenesis will be the central theme of a new research collaboration involving multiple NIH institutes.

In an aggressive research program on type 1 diabetes, we have established unique, innovative, and collaborative research groups, clinical trial networks, and consortia, with an overarching group to standardize and coordinate their efforts. We are also working to overcome barriers that currently prevent widespread clinical research on islet transplantation to restore normal insulin-producing capacity to patients. In collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), we are establishing a national consortium to step up progress toward general clinical applicability of islet transplantation.

To spur research in digestive diseases, the NIDDK recently established a new Liver Disease Branch within its Division of Digestive Diseases and Nutrition. With expert external input, this Branch is now spearheading the development of a Liver Disease Research Action Plan under the auspices of the Digestive Diseases Interagency Coordinating Committee. As requested by the Congress, the NIDDK is submitting a report on actions taken by the NIH and other HHS components in response to recommendations from a Consensus Conference on hepatitis C. In other research, broad approaches are providing insights into the inflammatory bowel diseases—Crohn's disease and ulcerative colitis. Fundamental studies are shedding light on the development of pathways that control gut motility; integration of pain, motility and behavioral neural circuits; and gut inflammation.

For polycystic kidney disease (PKD), a research consortium has established the value of Magnetic Resonance Imaging for measuring kidney size. This advance portends dramatic improvements in assessing disease progression—a critical step in developing and evaluating new treatments. The HALT-PKD Network is testing a regimen designed to lower blood pressure and slow disease progression—the first of several clinical studies envisioned. A workshop on oxalosis and primary hyperoxaluria—an inherited cause of kidney stone disease—has identified future clinical research directions, which will apply emerging knowledge about underlying metabolic and genetic abnormalities. We have also launched or expanded initiatives on interstitial cystitis, urinary incontinence, and urinary tract infections, consistent with the scientific recommendations of the Strategic Plan of the Bladder Progress Review Group. A recently formed Interstitial Cystitis (IC) Epidemiology Task Force is guiding efforts in that area, as described in a requested report to the Congress.

TRANSLATION RESEARCH AND ROADMAP EFFORTS

Underpinning our disease-focused programs is an emphasis on "translation" research, which benefits patients directly by bringing the fruits of laboratory discoveries into the arena of clinical research, and by propelling the positive results of clinical trials into medical practice. In one promising pilot effort to speed the development of therapies for type 1 diabetes, we are building on an innovative mechanism established by the NCI called "Rapid Access to Intervention Development." We are also pursuing several translational efforts related to the NIH Roadmap for Biomedical Research. These include development of non-invasive methods for diagnosing and monitoring the progression of diabetes, kidney and digestive diseases; harnessing new technologies such as proteomics the study of proteins and their functions; as well as studying stem cells during human development and tissue repair. We are leading an NIH Roadmap initiative in "New Pathways to Discovery" by enhancing metabolomics—the study of networks within the cell, and constituents of the cell, such as carbohydrates, lipids, and amino acids. We are also playing a major role in Roadmap efforts to build "Research Teams of the Future" by spurring interdisciplinary research training. These efforts can benefit programs within the NIDDK mission by bridging scientific disciplines and catalyzing partnerships, such as collaborations between biomedical and behavioral researchers, which are so important to moving obesity research forward.

Today, I have presented a cameo of our many and diverse research efforts and plans. Our research momentum has never been greater, and our commitment to improving health remains clear and strong.

PREPARED STATEMENT OF DR. SHARON H. HRYNKOW

Mr. Chairman and Members of the Committee, I am pleased to present the President's Budget for the Fogarty International Center for fiscal year 2005, a sum of $67,182,000, which reflects an increase of $1,838,000 over the comparable fiscal year 2004 appropriation.

I welcome this opportunity to relate Fogarty's progress over the past year and proposed plans for fiscal year 2005. Programs at Fogarty, developed with the support and guidance of the Administration and this Committee, reflect our nation's enduring commitment to achieve "a healthy America, in a healthier world." These were the words of the late Congressman John E. Fogarty, Chairman of the House Appropriations Subcommittee from 1951 until 1967, and for whom the center is named. He championed research as the one truly global effort in which all nations can and will join as real partners.

The health challenges facing the United States are many. Among the communicable diseases, AIDS and tuberculosis continue to challenge even the most sophisticated public health interventions. SARS emerged in Asia and washed upon our shores, as did West Nile Virus several years ago. And the emergence of avian flu in Asia and the United States is a compelling tale that is a harbinger of probable Asian flu pandemics yet to come. All told, the infectious threats cost our economy dearly. And as chronic disease such as cancer, cardiovascular disease, and mental health disorders increase year after year in the United States and world-wide, both treatment and prevention efforts must be applied. These challenges are shared with communities around the world.

To address these challenges, Fogarty supports a broad range of research and training programs, each designed to tackle particular health problems shared by United States and foreign populations. Our particular focus is on improving the capacity of communities in poor settings to address health challenges. Accordingly, our emphasis has been on working with scientists and health professionals in low- and middle-income nations on shared health problems. Our programs identify research opportunities best addressed through international cooperation. Fogarty's efforts are multidisciplinary, embracing clinical, epidemiological, basic biomedical and social science research. They are multi-sectoral, closely coordinated with our sister institutes at NIH, the Centers for Disease Control and Prevention, and international organizations with health and development missions, including The World Bank and the World Health Organization. Moreover, the programs enhance foreign relations with governments and communities alike, and advance the historic humanitarian role of our nation. And importantly, our programs promote a global culture of science, founded on equal partnerships between scientists working across borders, in a culture of sharing of scientific information, peer review and sound management policies. Fogarty supports over twenty research and training programs in more than 100 countries, involving more than 5,000 scientists in the United States and abroad.

What follows is a selective summary of ongoing and planned Fogarty activities to support NIH international objectives and realize Congressman Fogarty's vision.

THE HIV/AIDS EMERGENCY

HIV/AIDS has exacted a profound human toll in the United States and abroad, reversed gains in child survival in many nations, and threatened the economic stability of emerging markets by reducing the number of working men and women. Reducing the impact of HIV/AIDS in resource-poor countries, which bear the disproportionate burden of this disease, requires a strong national commitment on their part and international research cooperation to develop effective prevention and control strategies. The Fogarty AIDS International Training and Research Program (AITRP), now in its 16th year of operation, has been a major source of support for training a cadre of foreign medical scientists from developing countries needed to combat the global HIV/AIDS pandemic. Working through U.S. universities, Fogarty has supported Masters level, Ph.D., and post-doctoral training for young scientists in countries most affected by the pandemic. These scientists are testing HIV/AIDS vaccines abroad, developing effective public health strategies to reduce transmission, and acquiring new knowledge for treatment for those already infected.

Through the Fogarty AIDS Program, nearly 2,000 foreign researchers from over 100 countries have been trained in the United States, many at senior levels, and over 50,000 have trained in cutting-edge laboratory methodologies through workshops and courses conducted in those countries where HIV/AIDS is most devastating. This large international cadre of trained scientists has facilitated the implementation of new programs such as the Pediatric AIDS Foundation Call-To-Action, the President's initiative on prevention of maternal-to-infant transmission of HIV, and the President's Emergency Plan for AIDS Relief (PEPFAR). In addition, health scientists trained under the program have played vital roles in helping approximately 20 countries receive awards from the Global Fund for AIDS, TB and Malaria. As we work in partnership with colleagues around the world, the benefits of the Fogarty AIDS program accrue also in the United States. Interventions and

strategies developed and tested abroad may have direct relevance to communities in the United States.

Among research accomplishments in the past fiscal year, scientists at the University of North Carolina and the University of Malawi have identified a new and effective means to minimize postpartum transmission of HIV through implementation of an inexpensive two-drug antiretroviral regimen. This is of significance because low-income women in sub-Saharan Africa typically do not obtain medical attention during pregnancy and are usually uninformed of their HIV status until delivery. Effectively deployed, this intervention will mean that more newborn infants will have a chance to grow to be healthy adults, even where the lack of resources and other obstacles to extending medical care limit prenatal care and interventions.

CHANGING MICROBIAL THREATS

HIV/AIDS is a cautionary example. The rapid emergence of new pathogens and re-emergence of infectious disease, believed to have been controlled or contained, presents a disturbing new chapter in the grim evolutionary battle between humans and microbes. This is the result of social and demographic trends, including increases in international travel and trading across borders, and changes in the genetic structure of microbes that increase virulence and transmission, and weaken the efficacy of existing drugs. Among major disease pathogens, malaria has resurged due to resistance of the parasite to available drugs and resistance of mosquitoes to insecticides. Malaria accounts for an estimated 2 million deaths per year with increasing mortality due to drug resistance and HIV-contaminated blood transfusions related to malaria-induced anemia.

Building on the success of the AIDS training program, Fogarty launched in 1996 the International Training and Research in Emerging Infectious Diseases, a training program which builds expertise in microbiology, epidemiology, and laboratory methods as part of a broad effort to combat new and emerging diseases worldwide. Today, that program has been expanded to include other infectious diseases as the Global Infectious Disease Research Training Program, linking U.S. universities with counterparts around the world to advance research projects (through 27 Fogarty awards) and, importantly, to build the next generation of scientists able to combat emerging infections, such as SARS and West Nile Virus. Through this program, Fogarty is helping to address the infectious disease challenges of today while preparing for new pathogens yet to emerge tomorrow, as surely they will.

A powerful new tool for malariologists and other infectious disease researchers concerns the use of sophisticated mathematics to predict the course of an epidemic. Such mathematics, sometimes termed models, can be used to chart the benefits of prevention and control measures. Most recently, mathematical models were used to project the course of the SARS epidemic in Asia, and to develop strategies to limit the spread of the disease. Several years ago, Fogarty established a unit at NIH concerned with the use of mathematical models for control and prevention of several diseases, including malaria. The elements of a malaria prevention program include reducing the population of mosquitoes, treatment of malaria patients, and use of personal protection such as bed nets to prevent mosquito bites. In addition, there is a major effort underway to develop a malaria vaccine. The Fogarty epidemiologists have used mathematical models to determine the best strategy to employ such a vaccine, when it becomes available, along with existing methods of malaria control and prevention. All this must be done within the various complex ecological settings in which malaria occurs. The use of such advanced mathematics in devising the most effective strategies in the study of infectious diseases will surely bring unexpected benefits to human kind. Importantly, through a network of in-house research experts and extramural scientists, Fogarty also employs mathematical models to assist biomedical research and public health policy-makers prepare for and respond to bioterrorism events. In coordination with DHHS, Fogarty has mobilized experts in epidemiology, terrorism-response and public health policy in the context of category A agents including plague, tularemia smallpox and anthrax.

THE EMERGING EPIDEMICS OF CHRONIC DISEASE

By the year 2020, chronic disease is expected to contribute 60 percent of the global disease burden. The toll in the United States is already enormous: for example, obesity has more than doubled from 15 percent during 1976–1980 to 31 percent in 1999–2000, and 65 percent of adults ages 20 to 74 were overweight to obese in 1999–2000. As populations age, and risk exposures shift due to environmental and dietary factors, non-communicable diseases are estimated to become a leading source of disability and premature death in developing nations as well. Tobacco-caused disease and death is a major concern in the United States and globally. In

the United States, while picking up the habit of smoking is on the decline in most groups, in young girls it is on the rise (The World Bank). In low- and middle-income nations, as wealth increases in urban settings, smoking commencement in youth, and particularly in girls, is rising at alarming rates (The World Bank). To address this challenge, Fogarty launched in 2002 its International Tobacco and Health Research and Capacity Building Program. While in its early stages, our expectation is that research will lead to new interventions that will benefit U.S. communities as well as those around the world.

There is a growing awareness of the burden on health inflicted by trauma and injury both in the United States and worldwide. The numbers are startling: more than 1.2 million people are killed in traffic accidents annually, and millions more are injured or disabled. Deaths from all types of injuries, including war and domestic violence, are projected to rise from 5.1 million in 1990 to 8.4 million in 2020, with road traffic injuries as a major cause for this increase, with millions more sustaining injury that results in life-long disability. In response to the growing epidemic of trauma, Fogarty is initiating a new research and training program. Among the features of the program will be training across the range of basic to applied sciences, the epidemiology of risk factors, acute care and survival, rehabilitation, and the long-term mental health consequences. Possible research areas will include development of low-cost synthetic blood products and diagnostic imaging tools, identification of behavioral intervention strategies, particularly in youth and other high-risk groups, and health services research to determine cost-effective measures for emergency care in low-income settings. The new knowledge from the program will benefit not only developing countries but, as low-cost and effective strategies are identified, communities in the United States.

PREPARING THE NEXT GENERATION OF U.S. GLOBAL HEALTH LEADERSHI

While Fogarty works to build capacity and train young scientists in the developing world, critical steps have been taken to ensure that U.S. investigators at a formative stage in their careers also have opportunities to engage in international research projects. The Center will enhance and expand two programs to bring the next generation of U.S. scientists more fully into the global culture of science. The first of these, the International Research Scientist Development Award (IRSDA) program, provides post-doctoral training for four years, two of which must be spent conducting research in a developing country. Nearly 20 U.S. scientists are now being supported as IRSDA trainees. Addressing an earlier step in the career path, Fogarty has recently teamed with the Ellison Medical Foundation to create a second program, the new pre-doctoral clinical research training program for U.S. medical and public health students. Under this program, students will spend a year in a developing country conducting NIH-sponsored clinical research under the mentorship of an experienced foreign investigator and a collaborating research team. The first students to be selected will begin the program this summer.

ENHANCING OPPORTUNITIES FOR WOMEN IN SCIENCE

NIH's goal to bolster the nation's intellectual capital includes attracting more women to careers in science, both to build a new generation of talented scientists and to ensure that research issues germane to women's health are addressed. Fogarty has extended this important goal to international programs. At an October 2003 colloquium on career path issues facing women in the life sciences, including women in the developing world, Fogarty and its co-sponsors, the NIH Office of Research on Women's Health and the National Institute of Environmental Health Sciences, invited perspectives on opportunities in advancing career issues for women in the life sciences from a community of scientists, administrators and science funding agencies. To follow up on the recommendations, Fogarty and its partners have agreed to: collect data on developing country women in science and their career paths; support workshops to develop skill sets for women scientists in the developing world that will better enable them to take on leadership roles within health research and/or policy settings; and develop and implement strategies to effectively use the Internet and other information technologies to support networking and mentorship.

ADVANCING THE NIH ROADMAP: GLOBAL POSITIONING

Fogarty supports programs linked to each of the three main Roadmap themes—New Pathways to Discovery, Research Teams of the Future, and Re-Engineering the Clinical Research Enterprise. In particular, to improve the clinical research enterprise, Fogarty supports two new programs aimed at training developing country professionals in clinical, operational and health services research. These programs rep-

resent a new approach to enhance clinical research, and pave the way for new partners, namely those in low- and middle-income nations, to work more closely on mental health, and on AIDS and TB with U.S. counterparts. In support of Roadmap themes of new approaches and new pathways to discovery, Fogarty is also supporting studies to identify the impact of environmental degradation on economic development and human health. These programs link social scientists, including mathematicians and economists, with clinicians and medical researchers to provide new insights and strategies to tackle urgent global health challenges.

CONCLUSION

Mr. Chairman, global challenges require a global response. Collective action is not only an economically rational approach to global health research challenges, but a scientific and humanitarian imperative. With the continued support of this Committee, Fogarty will accelerate both research discoveries and applications through international cooperative action to the benefit of the United States and to global communities. "A healthy America in a healthier world" has never been as important as it is today. 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) of the National Institutes of Health (NIH). The fiscal year 2005 budget includes $297,647,000, an increase of $8,817,000 over the fiscal year 2004 enacted level of $288,830,000 over the comparable fiscal year 2004 appropriation.

The NIBIB's mission is to improve human health by leading the development and accelerating the application of biomedical technologies. The Institute is committed to integrating the physical and engineering sciences with the life sciences to advance basic research and health care. Our vision is to profoundly change healthcare by pushing the frontiers of technology to make the possible a reality.

PROGRESS TOWARDS SUCCESS

Established by law in December 2000, the NIBIB has already demonstrated an impressive track record as a conscientious steward of public funds and has achieved significant milestones. In fiscal year 2003 the NIBIB funded approximately 750 awards, including 300 new awards that received outstanding scores in a highly competitive peer review system. Consistent with our mission, approximately one-third of our new awards were for innovative, high-impact, though high-risk, exploratory studies. These studies addressed the feasibility of a novel avenue of investigation and/or breakthroughs in biomedical imaging and bioengineering within a specific area. The Institute has also been effective at reaching segments of the scientific community that traditionally have not been supported by the NIH, especially those from the engineering and quantitative sciences. Between the first and second years of our grant-making authority, proposals to the NIBIB from first-time NIH applicants increased significantly. In fiscal year 2003, approximately 50 percent of respondents to requests for targeted applications identified themselves as first-time NIH applicants.

The Institute has built a solid research infrastructure through the issuance of numerous basic and applied research solicitations in promising areas of scientific investigation. Responses to the Institute's targeted initiatives far exceeded even the most optimistic estimates based on prior NIH experience. Coupling this to the successful outreach to new applicants and to the science community, it is clear that NIBIB is filling an important need with regard to catalyzing interdisciplinary science and supporting engineering research aimed at translating scientific discoveries to practical applications.

The NIBIB continues to foster successful linkages and collaborations with other NIH Institutes and Centers, Federal agencies, academic institutions, and private industry. We regard input from industry as critical for helping to identify research needs that will result in significant healthcare improvements as well as for translating technologies and research results to patient applications. As a first step in establishing collaboration with the biomedical industry, the NIBIB sponsored a workshop on "Biomedical Industry Research and Training Opportunities" in December 2003. Recommendations from this meeting will be considered in the planning and development of future NIBIB programs.

ADVANCING TOMORROW'S TECHNOLOGIES TODAY

Biomedical imaging and bioengineering are interdisciplinary fields requiring 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 treating disease, and improving 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, orthopedics, and cardiology.

The quest for faster and more effective minimally invasive surgical interventions has resulted in the introduction of computer-assisted robotic technology, whereby the surgeon works with small tools through small incisions. However, current instrumentation prohibits the surgeon from actually feeling the forces exerted when manipulating tissue. This lack of sensory control can be particularly detrimental in surgery, where the forces applied to sutures are critical in creating knots that are strong enough to hold, but do not damage the tissue. To overcome this problem, NIBIB investigators are developing instruments with three-dimensional sensors designed to give the surgeon a feeling comparable to that of performing the task manually. This research has additional applications as well, including expert-assisted surgery in remote locations.

Magnetic resonance imaging (MRI) has been used successfully for over 15 years to generate soft tissue images of the human body. However, a number of diagnostic MRI applications require further improvements in both imaging speed and spatial resolution. For example, accurate abdominal imaging generally requires a complete image obtained during a single "breath-hold" period, which can take up to 30 seconds. Many patients, especially those with respiratory illnesses, cannot tolerate long breatholds. The NIBIB supports an active research program on optimizing MRI speed and spatial resolution. One new approach under study, called parallel imaging, collects MRI signals from a number of independent coil shaped antennas. The appropriate combination of these signals can provide an order of magnitude improvement in imaging speed or resolution. Enhancements such as this hold promise for greatly enhancing the non-invasive diagnosis and treatment of abdominal and neurological diseases.

Functional magnetic resonance imaging (fMRI) is a relatively new technique that builds on the basic properties of MRI to measure quick and tiny blood flow related metabolic changes that take place in the active brain. Thus, fMRI studies are capable of providing not only an anatomical view of the brain, but a minute-to-minute recording of actual brain activity. This technology is now being used by NIBIB researchers to precisely map functional areas of the normal, diseased, and injured brain and to assess risks associated with surgery or other invasive treatments. Functional MRI can help physicians determine exactly which parts of the brain are responsible for specific crucial functions such as thought, speech, movement, and sensation. This information allows physicians to better plan surgeries and radiation therapies and to guide interventional strategies for a variety of brain disorders.

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 and "highlight" defined cellular targets, will allow this technique to be more broadly applied to biomolecules that are known indicators of a diseased state. For example, NIBIB researchers have developed nanometer sized fluorescent crystals, called quantum dots, that glow and can act as markers for specific cells when bound to certain targeting agents such as cancer cell antibodies. These agents can more precisely pinpoint the location of the sentinel lymph node in breast cancer patients. The sentinel node (SN) is the first node in the body to come into contact with cancer cells as they leave the breast and begin to spread to the rest of the body. Testing for metastatic cancer cells in the SN allows for accurate staging using information from a single lymph node, rather than 10 to 15 axillary nodes, and allows patients to avoid many of the complications and side effects associated with a traditional axillary lymph node dissection.

Advances in bioinformatics have been identified as having great potential for positively impacting medical science and health care. NIBIB researchers are developing and evaluating several innovative technologies designed to help solve the information management problems faced by today's doctors. Concepts enveloped in this system include a medical record architecture designed for portability; a mechanism for

linking laboratory findings with medical problems; and a real-time, context-sensitive visualization of the medical record. Taken together, these concepts form a comprehensive system for facilitating evidence-based medicine in a real-world setting.

NEW BIOMATERIALS FOR TISSUE ENGINEERING

Tissue engineering holds the promise to repair and/or replace damaged organs using biologic materials. For success in this area, a number of scientific and bioengineering challenges must first be met. For example, we must learn to produce, manipulate, and deliver collections of cells not only as building blocks for tissues and organ systems, but as models for studying drug development. Toward this goal, NIBIB researchers have successfully transformed adult rat engineered tissue cells into cells that form cartilage and bone. The two cell types were integrated into separate layers, encapsulated in a gel-like biocompatible material, and shaped into the ball structure of a human jaw joint. Although more work is needed before this tissue-engineered joint can be used in humans, it holds great potential for treating patients with temporomandibular disorders, osteoarthritis, and rheumatoid arthritis. These procedures could also be further refined and adapted for developing artificial knee and hip joints.

Coronary stents are small devices that serve as a scaffold to prop open the inside of an artery and provide vessel support. They are commonly made of stainless steel or nylon mesh and therefore remain as a permanent implant in a blood vessel. Although stents have revolutionized the treatment of coronary artery disease, limitations include an inflammatory reaction and the development of stent closure due to blood clots forming within the device, a process termed restenosis. To address this problem, NIBIB researchers have recently developed a mechanically strong, hemocompatible, and X-ray visible polymer as a noninflammatory fully-degradable coronary stent. While designed as a stent, work continues to refine the device to serve additionally as a drug-delivery vehicle. This may also have application as a drug-delivery mechanism for other diseases, such as cancer.

SENSORS FOR MEDICINE

Biosensors are nanoscale or microscale devices that detect, monitor, and transmit information about a physiological change, or indicate the presence of various chemicals, gases, or biological materials. Laboratory diagnostics used in hematology, clinical chemistry, pathology, and microbiology already employ sensor technologies to perform simultaneous measurements for many substances in urine, blood, saliva, sweat, and interstitial fluids. The Institute has an active research program in sensor technologies and continues to expand this important area. For example, NIBIB researchers are engineering recombinant antibody fragments (recAbs) that will increase the sensitivity and specificity of a type of biosensor called a piezoimmunosensor. Piezoimmunosensors have been proposed for almost 20 years; however, there has been no procedure for providing a sensing layer that is uniform, chemically stable during the measurement process, and contains high numbers of binding sites. By creating tightly packed monolayers of recAbs that will bind to the surface of the sensing unit, researchers are solving this problem while also preventing non-specific interactions with molecules, and thus improving specificity.

Other researchers are focusing on the design and fabrication of miniaturized implantable responsive drug delivery devices that integrate a smart drug delivery system with a biosensor. These drug delivery systems are aimed at providing individualized therapies that monitor the patient's body chemistry and control drug flow as needed.

NIH ROADMAP

To transform the Nation's medical research capabilities and to speed the movement of research discoveries from the bench to the bedside and into medical practice, the NIH has laid out a series of far-reaching initiatives known collectively as the NIH Roadmap for Medical Research. The NIH Roadmap focuses on the most compelling opportunities in three main areas: new pathways to discovery, research teams of the future, and re-engineering the clinical research enterprise.

The NIBIB mission also strongly supports the NIH Roadmap initiative, since the Roadmap goal is to facilitate the development of innovative, novel and multidisciplinary science and technology that has the potential to further advances in health care. For example, the NIBIB is participating in an initiative that will facilitate the formation of collaborative research teams capable of generating novel probes for molecular and cellular imaging. The overall goal is to establish programs to create complete tool sets for the detection of single molecule events in living cells and to gen-

erate new strategies for dramatically increasing the imaging resolution of dynamic cellular processes.

Other areas of immediate interest to and supported by the NIBIB include the development of nanomedicine technologies, new tools for the study of proteomics and metabolic pathways, data and techniques for computational biology, and advances in bioinformatics. The NIBIB also strongly supports the NIH Roadmap theme on research teams of the future through sponsoring multidisciplinary research and interdisciplinary training.

MULTIDISCIPLINARY RESEARCH TEAMS

The value of collaboration among disciplines and organizations has long been recognized as important for developing novel approaches to problems in biology and medicine, and for effectively translating research results to patient applications. We are pleased to report that there have already been some successful "NIBIB partnerships" between biomedical engineers and imaging scientists that have had significant impacts on healthcare. For example, an ongoing Bioengineering Research Partnership team is using fMRI to integrate information on the suspected location of brain seizures with information about surrounding brain function in order to improve surgical outcome and reduce or eliminate seizures. In one early phase study, surgery employing fMRI strategies was used to almost eliminate seizures in a patient who had been suffering from as many as 100 seizures daily.

In conclusion, the NIBIB is dedicated to promoting the development of emerging technologies and interdisciplinary collaborations that drive healthcare advances. I would be pleased to respond to any questions that the Committee 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 2005, a sum of $2,930,397,000 an increase of 5,000 above the comparable fiscal year 2004 appropriation.

The NIH represents the largest and most significant public investment in AIDS research in the world a comprehensive program of basic, clinical, and behavioral research on HIV infection and its associated opportunistic infections and malignancies. 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.

WORLDWIDE PANDEMIC

AIDS is the deadliest epidemic of our time. More than 22 million people have already died of AIDS—3 million of them in 2003 alone—the largest number ever. HIV has already infected more than 60 million people around the world, and AIDS has surpassed tuberculosis and malaria as the leading infectious cause of death worldwide.[1]

The United Nations General Assembly's Declaration of Commitment on HIV/AIDS states ". . . the global HIV/AIDS epidemic, through its devastating scale and impact, constitutes a global emergency and one of the most formidable challenges to human life and dignity, as well as to the effective enjoyment of human rights, which undermines social and economic development throughout the world and affects all levels of society national, community, family, and individual."[2] According to a U.N. report, "The epidemic has not only killed people; it has imposed a heavy burden on families, communities and economies. The misery and devastation already caused by HIV/AIDS is enormous, but it is likely that the future impact will be even greater . . . The HIV/AIDS epidemic has erased decades of progress in combating mortality and has seriously compromised the living conditions of current and future generations. The disease has such a staggering impact because it weakens and kills many people in their young adulthood, the most productive years for income genera-

[1] "Report on the Global HIV/AIDS Epidemic: July 2002," (UNAIDS/WHO, Geneva, Switzerland, 2002).

[2] "The Impact of AIDS" (Department of Economic and Social Affairs, United Nations, 2003).

tion and family caregiving. It destroys families, eliminating a whole generation crucial for the survival of the younger and older persons in society." The report also highlights "the long-term damage accruing to human capital, as children's education, nutrition and health suffer directly and indirectly as a consequence of HIV/AIDS. The effects of lowered investment in the human capital of the younger generation will affect economic performance for decades to come, well beyond the timeframe of most economic analysis."[3] Another dimension to the epidemic in Africa was cited in the New York Times: "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."[4]

A recent CIA report estimated that by 2010, 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.[5] 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."[6] Dramatic increases in HIV infection also are occurring in Eastern Europe, Central Asia, Latin America, and the Caribbean.

THE U.S. EPIDEMIC

According to CDC, the decline in death rates observed in the late 1990s, due largely to expanded use of new antiretroviral therapies (ART) that prevent progression of HIV infection to AIDS, has now leveled off; and AIDS incidence increased 2 percent in 2002 (over 2001). This means that the overall epidemic is continuing to expand.[7][8][9] 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. HIV infection rates are continuing to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people over 50 years of age.[10] The appearance of multi-drug resistant strains of HIV presents an additional serious public health concern.[11][12][13][14][15] According to CDC reports, approximately one quarter of the HIV-infected population in the United States also is infected with hepatitis C virus (HCV). HIV/HCV co-infection is found in 50 to 90 percent of injecting drug users (IDUs). HCV progresses more rapidly to liver damage in HIV-infected persons and may also impact the course and management of HIV infection, as HIV may change the natural history and treatment of HCV.[16] 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 aca-

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[3] Ibid.
[4] A. de Waal, "What AIDS Means in a Famine," New York Times, 11/19/02.
[5] "Intelligence Community Assessment: The Next Wave of HIV/AIDS: Nigeria, Ethiopia, Russia, India, and China." (CIA, 2002).
[6] "The Future of AIDS," Foreign Affairs, November/December 2002.
[7] CDC Year-End HIV/AIDS Surveillance Report for 2002 (CDC, 2003).
[8] "Centers for Disease Control and Prevention HIV Prevention Strategic Plan Through 2005," (CDC, 2001).
[9] "HIV/AIDS Update—A Glance at the HIV Epidemic," (CDC, 2001).
[10] "U.S. HIV and AIDS Cases Reported Through June 2000," CDC HIV/AIDS Surveillance Report, Vol. 12 (2002).
[11] N. Loder, Nature 407, 120 (2000).
[12] H. Salomon et al., AIDS 14, 17 (2000).
[13] Y.K. Chow et al., Nature 361, 650 (1993).
[14] M. Waldholz, "Drug Resistant HIV Becomes More Widespread," Wall Street Journal, 2/5/99.
[15] "World Health Report on Infectious Diseases: Overcoming Antimicrobial Resistance," (WHO, Geneva, 2000).
[16] "Frequently Asked Questions and Answers About Coinfection with HIV and Hepatitis C Virus" (CDC, 2002).

demia, 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 planning process also serves to monitor and assess scientific progress on an annual basis.

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.

VACCINES AND PREVENTION RESEARCH

Vaccine research remains a critical priority. 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, approximately 14 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. The development of vaccine candidates also requires sufficient quantities of non-human primates for preclinical testing.

In addition to vaccines, our biomedical prevention research priorities include the development 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.

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 that 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 resist-

ant 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.

INTERNATIONAL RESEARCH

NIH bears a unique responsibility to address the urgency of the global AIDS epidemic. To meet that need, 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.

SUMMARY

The human and economic toll of the AIDS pandemic is profound, demanding a unique response that is complex, comprehensive, multi-disciplinary, and global. The NIH role in this response is fundamental and unprecedented. The nation's investment in AIDS research is reaping even greater dividends, as AIDS-related research is unraveling the mysteries surrounding many other infectious, malignant, neurologic, autoimmune, and metabolic diseases. The authorities of the OAR allow NIH to pursue a united research front against the global AIDS epidemic. We are deeply grateful for the continued support the Administration and this Committee have provided to our efforts.

PREPARED STATEMENT OF DR. FRANCIS S. COLLINS

Mr. Chairman, I am pleased to present the President's budget request for the National Human Genome Research Institute for fiscal year 2005, a sum of $492,670,000, which reflects an increase of $13,842,000 over the fiscal year 2004 Final Conference appropriation.

Following the completion of the Human Genome Project last year, the National Human Genome Research Institute (NHGRI) of the National Institutes of Health announced an ambitious plan for applying genomics to human health benefits. *A Vision for the Future of Genomics Research*, the outcome of almost two years of intense discussions with over 600 scientists and members of the public, has three major areas of focus: Genomics to Biology, Genomics to Health, and Genomics to Society. Several ambitious projects are already underway to help achieve this vision includ-

ing the International Haplotype (HapMap) Project, the Encyclopedia of DNA Elements (ENCODE), the NIH Roadmap initiative on Molecular Libraries, and a new Ethical, Legal and Social Implications (ELSI) Center initiative. As we enter the genomic era, the continued support of biomedical research in this area is more vital than ever.

ONGOING NHGRI INITIATIVES

International HapMap Project

To study genetic variation more effectively across the human genome, the NHGRI and a team of partners has launched the International HapMap Project. The goal of the project is to determine the common patterns of DNA sequence variation in the human genome, and to make this information freely available in the public domain. This international consortium is developing a map of these patterns across the genome by determining the genotypes of one million or more sequence variants in DNA samples from populations with ancestry from Africa, Asia, and Europe. When complete, the HapMap will enable the discovery of sequence variants that affect common disease, the development of diagnostic tools, and the ability to choose targets for therapeutic intervention. Detailed information about the HapMap project was published in a landmark article in *Nature*, and updated details can be found on the web at www.hapmap.org.

Comparative Genomics to Understand the Human Genome

One of the most powerful approaches for unlocking the secrets of the human genome is comparative genomics. While the completed sequence of the human genome represents a milestone of historic proportions, a daunting challenge that still lies ahead is to interpret its biological meaning and function. Recently sequenced genomes of the mouse, rat, and a wide variety of other organisms—from yeast to chimpanzees—prove that the genomes of other species are amongst the most powerful tools in advancing understanding of the human genome. The current NHGRI-supported, large-scale sequencing centers have built a prodigious capacity for, and expertise in, sequencing entire genomes. The combined capacity of these centers is expected to yield the equivalent of about 20 additional draft vertebrate genomes in just the next three years. These additional species sequences will provide exciting new insights into the function of the human genome, and will assist genome scientists in translating the basic findings of the Human Genome Project into tangible applications, including the diagnosis, prevention, and treatment of disease.

ENCODE—ENCyclopedia Of DNA Elements

To understand the meaning of the human instruction book, the genome, the identities and precise locations of all functional elements must be determined. Thus, the NHGRI has launched the ENCyclopedia Of DNA Elements (ENCODE) project to identify these elements comprehensively. The ENCODE project seeks to characterize the tools needed for exploring genomic sequence, improve those tools when necessary, and define a clear path for the determination of all of the functional elements in the entire human genome. On October 9, 2003, the NHGRI announced the first ENCODE grants in a three-year, $36 million project (www.genome.gov). ENCODE begins as a pilot effort to evaluate methods for the exhaustive identification and verification of functional sequence elements in a carefully selected 30 million base pairs, or about one percent, of human genomic DNA. This will require access to information, resources, ideas, expertise, and technology beyond the capabilities of any single group. Therefore, a consortium of investigators with diverse backgrounds and expertise will work cooperatively to carry out this project to: (1) evaluate rigorously the relative merits of a varied set of computational and experimental techniques, technologies, and strategies for identifying the functional elements in human genomic sequence, and (2) test the capabilities of such methods to scale up efficiently to allow, ultimately, analysis of all the functional elements encoded in the entire human genome sequence.

Centers Of Excellence In Genomic Science (CEGS)

The NHGRI Centers Of Excellence In Genomic Science (CEGS) program has been in place for four years. This program is a centerpiece of the Institute's effort to stimulate new interdisciplinary approaches to genomic research and technology development. A total of about 10 CEGS grants are ultimately expected to be funded. These will generally be five-year awards of up to $3 million per year. Seven awards have been made to date; each involves multiple investigators and disciplines, and several cut across departments and institutions. A grantee meeting in October 2003 stimulated new collaborations and identified ways to share CEGS grant data and resources with the larger research community.

Clinical Research Activities in the NHGRI Intramural Program

Research efforts of NHGRI Division of Intramural Research (DIR) investigators are aimed at deciphering the genetic contributions to common disorders, to provide a better understanding of diseases such as cancer, diabetes, and heart disease, as well as to a number of less common but equally debilitating afflictions. DIR investigators have been at the forefront of scientific innovation, developing a variety of research approaches that accelerate the understanding of the molecular basis of disease. These include the development of DNA microarray technologies for large-scale molecular analyses, innovative computer software to study fundamental biological problems, animal models critical to the study of human inherited disorders, and the clinical testing of new therapeutic approaches for genetic disease. Three examples of gene discoveries within the past year include the gene responsible for Hutchinson-Gilford progeria syndrome, the disease causative gene for Charcot-Marie-Tooth disease type 2D, and a gene variant that contributes to the risk of type 2 diabetes. These and other advances should ultimately lead to improved diagnostic, prevention, and treatment strategies having a direct impact on human health.

NEW INITIATIVES

The NHGRI is very enthusiastic about the initiatives included in the NIH Roadmap and is deeply involved in implementation plans for several of the projects embodied in the "New Pathways to Discovery" theme.

Molecular Libraries

As part of its *Vision for the Future of Genomics Research*, and in partnership with many other NIH Institutes as part of NIH's new Roadmap for Medical Research, the NHGRI is taking a lead role in providing access to high throughput screens for small organic molecules to public sector researchers. These small molecules can be used as chemical probes to study cellular pathways in great depth and will broadly enable public and private biomedical research into basic biology and accelerate the validation of new therapeutic targets, and thus the discovery of new drugs. For this effort to provide maximal benefits, the library of small molecules must contain a sufficient number of compounds. To build such a library, a network of six national centers will establish a common collection of 500,000 or more chemically diverse small molecules, of both known and unknown activities. Investigators who develop assays suitable for high throughput screening will apply for access to these centers. After peer review, suitable assays will be run through a screen of 500,000 or more compounds, and the positives subjected to a first pass of chemical optimization to generate useful compounds. We anticipate that this new resource will catalyze a genuine paradigm shift, because it will give academic investigators a new and powerful research tool not previously at their disposal.

$1,000 Genome Sequence

Current sequencing costs are too high to collect the quantity and quality of soome sequences optimal for research and clinical applications. Completely sequencing the genomes of many individuals would greatly advance understanding of the role of DNA sequence variation in human health, but using DNA sequence information for care of individuals is not possible at current costs. Thus, NHGRI has launched an aggressive program to develop technologies to lower the cost of DNA sequencing dramatically. The goal for the first five years of this program is to develop the capability to produce a high quality draft sequence for a large, complex (e.g., mammalian) genome for $100,000. The goal of the second phase, which is estimated to take ten years, is producing a genome sequence for $1,000. Once achieved, a $1,000 genome analysis would be of great use to correlate DNA information with health outcomes. This includes determining genes in each individual that predispose that individual to specific diseases, and assessing which drugs are likely to elicit adverse reactions in each individual, so that drugs can be used more effectively and with fewer side effects.

Centers for Excellence in ELSI Research

The NHGRI Ethical Legal and Social Implications (ELSI) research program recently released a Request for Applications inviting proposals for the development of Centers of Excellence in ELSI Research (CEER). The CEER program is designed to support the development of groups that will pursue research questions best approached through intensive and extended collaboration among investigators from multiple disciplines, using diverse methodologies. CEER investigators are encouraged to consider new ways to explore these questions, design innovative and efficient research projects, propose and disseminate health or social policy options based on Center research, and, when feasible, facilitate policy development perti-

nent to a specific issue. Center applicants are particularly encouraged to identify cutting edge research topics and approaches that may lead to high payoff solutions to important ELSI problems.

Intramural Social and Behavioral Research Branch

The NHGRI has formed a new Social and Behavioral Genetics Research Branch within its intramural research program. The main focus of the Branch is to conduct research on the social and behavioral aspects of translating genomic discoveries into improved health. The Branch will also: (1) study innovative ways of applying genetic discoveries to promote health and well-being; (2) apply social, behavioral, and communication theories to understand how to communicate genetic risk effectively; (3) develop and refine evidence-based methods of communicating genetic risk to individuals, families, communities, and populations; (4) seek to understand how social factors influence genetic discoveries and research; and (5) investigate the ethical and public policy implications of genetic research and the use of genetics in clinical practice.

OTHER AREAS OF INTEREST FOR NHGRI

Genetic Discrimination

The NHGRI remains concerned about the risk of genetic discrimination and supports the President's call for federal legislation. Many Americans are worried that insurers and employers may use genetic information to deny, limit, or cancel their health insurance or to discriminate against them in the workplace. A total of 41 States have enacted legislation on discrimination in health insurance and 31 have enacted legislation on workplace genetic discrimination. However, only comprehensive federal legislation can guarantee everyone in the United States protection from genetic discrimination. Last October, the full U.S. Senate voted unanimously (95–0) in favor of the "Genetic Information Nondiscrimination Act of 2003" (S. 1053), which would address this problem. It is hoped that the House will soon take similar steps.

Intellectual Property Rights in Genetics and Genomics Research

NHGRI has long worked on issues of intellectual property related to genetic and genomic data. The NHGRI ELSI program plans soon to issue a new initiative to encourage studies of the role of intellectual property rights in genetics and genomics research, as well as the impact of exclusivity on progress in these fields. The initiative will support legal, economic, political science, and statistical analyses and empirical investigations of theories and practices of rights holders, stakeholders, and researchers in genetics and genomics research and development, with the specific goal of helping build the research base necessary to inform the rational development of future policy options regarding intellectual property in genetics, and genomics.

The NHGRI, with several other NIH Institutes, has recently provided funds for a National Academy of Sciences' study, "Intellectual Property in Genomic and Protein Research and Innovation." This 18-month study, involving experts from law, public policy and genomics, will address such important questions as: What is the impact of intellectual property and licensing on genetic and proteomic research? What policy options should be considered in this area? How have other regions of the world addressed these issues? It is hoped that this study will provide insights on how to address the thorny issues surrounding the interface of intellectual property, biomedical research, and patient care.

Direct-to-Consumer Marketing of Genetic Tests

Marketing of products or services that promise to provide consumers with genetic insights into personal health has proliferated dramatically in recent years. NHGRI's intramural Division of Bioethics has systematically studied this issue. So far, researchers have found that many direct-to-consumer (DTC) advertisements exaggerate the scientific basis of claims made and/or fail to communicate effectively the current limitations of the specific genetic knowledge discussed. In particular, the Internet has provided a powerful medium for the construction of "informational" resources through which DNA analysis is often linked to a claim to individualize consumer profiles for specific products available through the website. Additionally, the first example of a multi-media DTC advertising campaign for a genetic test, the BRCA1/2 test, was piloted in two metropolitan areas in the last year. The NHGRI recently held a workshop to assess DTC marketing of genetic tests, and considered the scope of the practice and possible policy options. The NHGRI will work with the Secretary's Advisory Committee on Genetics Health and Society on this issue.

Trans-NIH Obesity Initiative

The NHGRI Deputy Director represents the Institute on the trans-NIH obesity working group. We believe that this initiative is vitally important, and that the genomic tools produced by the Human Genome Project can be of considerable utility in discerning the role of genes and environment in causing obesity, and in predicting which obese individuals will develop which diseases.

CONCLUSION

With the completion of the human genome sequence, we have fully entered the genomic era. The NHGRI has now spearheaded many specific and innovative initiatives to understand how genetics affects human health, the ultimate motivation for the Human Genome Project. The most interesting and important applications of genomics lie not behind us, but ahead of us. Continued investment by the Congress in genetic/genomic research is vital to our efforts to enhance the health of all.

PREPARED STATEMENT OF DR. RICHARD J. HODES

Mr. Chairman and Members of the Committee: The NIA is requesting an fiscal year 2005 budget of $1,055,666,000, an increase of $31,068,000 or 3 percent over the comparable fiscal year 2004 appropriation.

Thank you for this opportunity to participate in today's hearing. I am Dr. Richard Hodes, Director of the NIA, and I am pleased to be here today to tell you about our progress making and communicating scientific discoveries that will improve the health and well-being of older Americans.

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: Studies confirm that disability among America's elders has declined steadily 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.

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. Over half of Americans over age 50 have osteoporosis or low bone mass. Cardiovascular disease, cancer, and diabetes remain common among older Americans. And as many as 4.5 million Americans suffer from Alzheimer's disease (AD), the most common cause of dementia among older persons.

The mission of the National Institute on Aging is to improve the health and well-being of older Americans through research. In support of this mission, the Institute conducts and supports an extensive program of research on all aspects of aging, from the basic cellular and molecular changes that occur as we age, to the prevention and treatment of common age-related conditions, to the behavioral and social aspects of growing older, including the demographic and economic implications of an aging society. In addition, the NIA is the lead federal agency on Alzheimer's disease research; our activities in that area encompass prevention, detection, clinical trials, and caregiver issues. Finally, our education and outreach programs provide vital information to older people across the United States on a wide variety of topics, including living with chronic conditions such as arthritis or diabetes, caring for a loved one with Alzheimer's disease, and maintaining optimal health through exercise.

The NIA works to rapidly translate research findings into practical interventions and information that will benefit older Americans. This may involve enhancing our methods of communicating important research findings to physicians or the public; creating opportunities for patients to benefit from groundbreaking research through participation in clinical trials; or even recognizing the potential of a very basic finding in a mouse, a worm, or a molecule to eventually have a powerful impact on the public health.

For example, recent findings in *C. elegans*, a tiny worm that is frequently used for genetic studies, are providing important insights about fat regulation and storage that may lead to improved understanding of overweight and obesity in humans. NIH-supported researchers used RNA interference (RNAi), a technique in which genes are inactivated one at a time to determine their function, to screen the worm's genome and found some 417 genes involved with fat regulation and storage. Many of the genes they found have human counterparts, a number of which had not been previously implicated in the regulation of fat storage. Overweight and obesity are

widespread in the United States and are associated with an array of health problems, including heart disease, stroke, osteoarthritis, adult-onset diabetes, and certain types of cancer; the genes identified in *C. elegans* may ultimately suggest new targets for treating human obesity and its associated diseases.

Another recent basic discovery, this one in mice, may have profound implications on the field of reproductive biology. Since the 1950s, scientists have believed that women are born with all the oocytes (eggs) they will ever have, and that these eggs die off as a woman ages, with fertility diminishing and, at menopause, disappearing as a result. However, NIH-supported researchers recently found that oocyte-containing follicles continue to develop in the ovaries of adult mice. If this finding is confirmed—and extended to humans—it could lead not only to new treatments for premature ovarian failure (which affects some 250,000 American women under age 40, according to the National Institute of Child Health and Human Development), but also to interventions to delay menopause and extend fertility.

NIA-supported investigators in all fifty states are conducting research that is changing the way we prevent, diagnose, and treat the diseases of aging. NIA also supports networks of centers that focus on specific topics, including demography and the basic biology of aging. There are currently 29 NIA-supported Alzheimer's Disease Centers (ADCs), at which investigators are working to translate research advances into improved care and diagnosis for AD patients while focusing on the program's long-term goal—finding ways to treat and possibly prevent AD. Many ADCs have satellite facilities that offer diagnostic and treatment services and collect research data in underserved, rural, and minority communities. Another type of Center, the Edward R. Roybal Centers for Research on Applied Gerontology, translates behavioral and social research findings into practical outcomes for older adults. Each of the six Roybal Centers addresses one or more central themes (e.g., cognitive influences on physician/patient interaction affecting medical compliance; safe driving behavior; social role adjustment upon retirement).

The NIA also supports a variety of clinical trials, frequently in collaboration with one or more NIH Institutes or other organizations. For example, NIA is currently supporting 25 AD clinical trials, seven of which are large-scale prevention studies. These trials are testing agents such as 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 to AD, NIA supports clinical trials for a number of other conditions, including cardiovascular disease, Parkinson's disease, and certain types of cancer.

A major clinical trial in which NIA-supported researchers took part is the Diabetes Prevention Program, a multi-institutional study that was initiated by the National Institute on Diabetes and Digestive and Kidney Diseases and was designed to identify interventions that could prevent or delay the development of type 2 diabetes. The researchers found that people who are at high risk for diabetes can sharply reduce their risk by adopting a low-fat diet and 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 the study participants to determine long-term effectiveness of these interventions.

The NIA also has a number of ongoing or planned special initiatives on diverse research topics. These include:

Health Disparities.—The NIA's Healthy Aging in Neighborhoods of Diversity Across the Lifespan (HANDLS) project is a community-based study of health disparities among different racial, ethnic, and socioeconomic groups in Baltimore. The purpose of HANDLS is to disentangle the effects of race and socioeconomic status on risk factors for morbidity and mortality, incidence and progression of pre-clinical disease, development and persistence of health disparities, longitudinal health status, and health risks. The pilot phase of the study was completed in December 2001, and the full-scope study is now being planned for implementation in 2004–2005. Unique to the HANDLS study is the use of two fully-equipped mobile research laboratories that enable investigators to collect data directly in the neighborhoods under study, establishing links with the community and increasing both the interest of potential participants and the retention rate.

Neuroimaging.—The NIA is developing an Alzheimer's Disease Neuroimaging Initiative, a longitudinal, prospective, natural history study of normal aging, mild cognitive impairment, and early AD to evaluate neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET). The study objectives are to:

—Identify the best markers for early diagnosis of AD
—Identify markers for following disease progression and monitoring treatment response
—Develop surrogate endpoints for clinical trials
—Decrease time and expense of drug development
—Establish methods for the collection, processing, and distribution of neuroimaging data in conjunction with other biological, clinical, and neuropsychological data

The initiative is planned as a partnership among the NIA/NIH, academic investigators, the pharmaceutical and imaging equipment industries, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the NIH Foundation, with participation from the Alzheimer's Association and the Institute for the Study of Aging. The clinical, imaging, and biological data and samples will be made available, with appropriate safeguards to ensure participant privacy, to scientific investigators in the academic and industrial research communities.

Testosterone replacement in men.—Levels of circulating testosterone decline as men age, and this decline may be related to decrements in physical and cognitive functioning—for example, recent research suggests that older men with lower levels of free, or unbound, testosterone circulating in their bloodstreams could be at increased risk of developing Alzheimer's disease (AD). Increasingly, middle-aged and older men are turning to testosterone replacement therapy (TRT) to forestall these symptoms: In 2002, over 800,000 men received some form of testosterone replacement. However, as with the use of hormone replacement therapy among women prior to the release of the Women's Health Initiative results demonstrating serious HRT-related risks, men are using TRT in the absence of clear scientific data supporting its use. A multi-disciplinary panel, led by the Institute of Medicine and supported by the NIA and the National Cancer Institute, recently evaluated the pros and cons of conducting clinical trials of testosterone replacement therapy in older men to answer many of the lingering questions about the effects of this hormone in the aging body. The NIA is considering the IOM recommendations very carefully and will act on the recommendations to begin clinical trials to determine the efficacy of testosterone in treating symptomatic older men with low testosterone levels.

Genetics.—The NIA has established a new AD Genetics Initiative, a program to accelerate the pace of AD genetics research by creating a large repository of DNA and cell lines from families with multiple AD cases. The goal of this initiative is to develop strategies for identifying the remaining late-onset AD (LOAD) risk factor genes, associated environmental factors, and the interactions of genes and the environment. The NIA's AD Genetics Initiative will intensify sample collection and encourage data sharing by providing access to the repository to qualified investigators. To date, several well-integrated components of the Genetics Initiative have been launched. Mechanisms to efficiently identify and share large numbers of samples for AD genetic analysis have been developed through the recently-enlarged National Cell Repository for AD (NCRAD), and eighteen of the NIA's Alzheimer's Disease Centers have received supplemental funding to recruit new family members participation. Uniform standards for sample collection have also been developed. As of late January, over 200 families have been evaluated and enrolled, and over 800 blood samples have been logged at NCRAD. A clinical task force has been established which is helping to determine the correct phenotypic data to be included with the biological samples. A major goal is the long-term follow-up of individuals participating in the study.

In order to publicize the initiative, the NIA Office of Communications and Public Liaison, together with its Alzheimer's Disease Education and Referral Center, Columbia University, and NCRAD, partnered with the Alzheimer's Association to conduct focus groups and develop publicity materials to help recruiting efforts. These publicity materials, including a workbook, CD ROM, fact sheet, and brochure were distributed at the a recent meeting of the ADCs and will now be sent to ADCs and Alzheimer's Association chapters to help recruiting efforts.

Longevity.—The NIA has formed a Longevity Consortium to help identify and understand genetic and other factors that predispose to human longevity or protect against multiple age-related conditions, a major goal in aging research. The Consortium is an innovative system for expeditious generation, review, and funding of new projects as opportunities arise, and includes epidemiologists, geneticists, population biologists, statisticians, and others with an interest in the genetic and molecular basis for longevity. Participants can draw on the study populations of 15 of the largest human aging studies, including the Cardiovascular Health Study, the Women's Health Initiative, Health ABC, the Study of Osteoporotic Fractures, the Rotterdam Study, the Honolulu Heart Study, and the New England Centenarian Study. Alto-

gether, Consortium researchers will have access to data on some 200,000 study subjects.

Demography.—As the percentage of Americans over age 65 increases, profound societal changes will likely occur. NIA-supported researchers are exploring the changing demographic, social, and economic characteristics of the older population. Research embraces topics such as: trends in the age-structure of populations; changes in levels of disease and disability; economic costs of disability; cost-effectiveness of interventions; migration and geographic concentrations of the elderly; decision-making about retirement; pensions and savings; the relationship between health and economic status; and health disparities by gender and race. The results of this research often have important implications for public policy. Such research often involves large datasets that are frequently co-sponsored by NIA and other government agencies in the United States and overseas. These include:

—*Health and Retirement Study*, a biennial survey of more than 22,000 Americans over age 50, which provides data for researchers, policy analysts, and program planners who are making major policy decisions that affect retirement, health insurance, saving and economic well-being.

—*National Long-Term Care Study*, which explores trends in the prevalence of self-rated old age disability and physical, cognitive, and sensory limitations.

—*Longitudinal Study of Aging*, a long-term study in which the NIA participates with the National Center for Health Statistics.

—*Panel Study of Income Dynamics*, begun in 1968 and conducted by the National Science Foundation, is a nationally representative longitudinal study that collects information on U.S. households. Notably, the PSID contains information on approximately 5,000 heads of households and spouses who are baby boomers (born 1945–1964)—a cohort not yet represented in the Health and Retirement Study (HRS). Continued data from the PSID will shed light on individual household saving behavior of the baby boom generation and its neighboring age cohorts.

Health Communication.—Communication of research-based health information is another key activity of the NIA, and the Institute uses both traditional and innovative means to disseminate information. In 2003, the Pew Internet and American Life survey found that 22 percent of Americans age 65 or older have access to the Internet, and that 58 percent of these "wired seniors" had used the Internet to look for information about a specific disease. However, NIA-supported research has demonstrated that with age come changes in cognition (such as working memory, perceptual speed, text comprehension) and vision (including loss of ability to detect fine details, less light reaching the retina, and loss of contrast sensitivity) that could hinder the older person's ability to use the Internet easily and effectively. To respond to the unique needs of Internet users over 60, the NIH launched NIHSeniorHealth.gov on October 23, 2003. Developed by the NIA and the National Library of Medicine, and featuring content developed in collaboration with several other NIH Institutes, this web site is easy for older adults to read, understand, remember, and navigate. For example, the site features large print and short, easy-to-read segments of information repeated in a variety of formats—such as open-captioned videos and short quizzes—to increase the likelihood it will be remembered. Consistent page layout and prompts help users move from one place to another on the site without feeling lost or overwhelmed. The site also has a "talking" function, which allows users the option of reading the text or listening to it as it is read to them.

The risk of many diseases increases with age, so the site focuses on health topics or specific diseases that are of particular interest to older people, including Alzheimer's disease, Alzheimer's disease caregiving, arthritis, balance problems, breast cancer, colorectal cancer, exercise for older adults, hearing loss, lung cancer, and prostate cancer. Upcoming and planned topics include complementary and alternative medicine, diabetes, falls, shingles, vision changes, and others. Each topic provides general background information, quizzes, frequently asked questions (FAQs), open-captioned video clips, transcripts for the videos, and photos and illustrations with captions. From its launch in October 2003 through late January, NIHSeniorHealth.gov has received over a million page views and been visited by nearly 118,000 unique visitors.

The NIA also maintains a large selection of lay-language Age Pages, which cover an array of topics relevant to older people and include information on a number of diseases and conditions, suggestions for coping with these conditions, and information on other resources. Most of the Age Pages have been translated into Spanish.

At a March 2002 hearing of this Committee entitled "Bench to Bedside," Chairman Regula recommended that NIA and the Administration on Aging (AoA) work together to disseminate research-based consumer education to the thousands of sen-

iors who participate in the Meals-on-Wheels program across the Nation. In response, NIA staff, with the participation of AoA, have conducted focus groups of program managers from the Meals on Wheels Association of America (MOWAA) to determine the types of information of greatest interest to MOW's clients, as well as the best ways to deliver such information (e.g., meal tray liners printed with key health messages, articles for MOWAA newsletters, or specially crafted Age Pages.) Based on focus group feedback, NIA is currently revising Age Pages on diabetes, alcohol, and depression; these materials will be tested at the upcoming MOWAA meeting in September 2004, and we anticipate that distribution to MOWAA clients will begin shortly thereafter.

The Alzheimer's Disease Education and Referral (ADEAR) Center has been compiling and disseminating information about AD for health professionals, persons with AD and their families, and the public since 1990. NIA is also working to translate research findings into action through its highly successful campaign to encourage older people to exercise. In the last four years, NIA has distributed over 611,000 copies of its exercise guide and 93,000 copies of its companion video to the public. A Spanish-language version of the guide was published in January 2002, and over 33,500 copies have been distributed to date. The NIA's efforts to promote exercise and strength training are conducted in support of the President's "HealthierUS" and the Department of Health and Human Services' "Steps to a HealthierUS" initiatives.

PREPARED STATEMENT OF DR. ANDREW C. VON ESCHENBACH

BUDGET STATEMENT

The fiscal year fiscal year 2005 budget includes $4,870,025,000, an increase of $134,052,000 over the fiscal year 2004 enacted level of $4,735,973,000 comparable for transfers proposed in the President's request.

2015 CHALLENGE GOAL

The Nation's unwavering support of cancer research has enabled the National Cancer Institute (NCI) and our many partners throughout the cancer research community to make enormous strides over the past three decades. Our understanding of cancer as a disease process, and the associated opportunities to prevent, detect early and successfully treat it has improved dramatically. However, even in the face of this progress, the magnitude of the cancer burden means that the disease still affects nearly every family in America. This year, approximately 1.4 million of our citizens will face a cancer diagnosis, and over 560,000 of our citizens—about 1,540 each day—will die from their disease. Furthermore, the fact that cancer occurs primarily in individuals over the age of 50 means that more of our citizens will suffer the terrible burden of this disease in the next 10–20 years due to the aging and changing demographics of our population.

Fortunately, the convergence of science and advanced technologies is changing our perceptions of what is possible. In fact, we are entering a period in biomedical research where progress in cancer research can be exponential—an inflection point. Last year I informed this committee that "our nation's investment in basic research has fueled the engine of discovery, which is rapidly illuminating the cumulative genetic changes and associated molecular mechanisms that ultimately produce cancer." As I said then and I reiterate now "for the first time, we have within our grasp the ability to design target-specific interventions to preempt this process." Based on the current astounding pace of progress in cancer research and the transformational effects of advanced biomedical technologies, I am even more fervent in my belief that we can achieve this vision.

To capitalize on this inflection point, I have set forth an ambitious challenge goal for the NCI, and for the entire cancer research and care community: to eliminate suffering and death from cancer by 2015. This "stretch goal" is intended to unify and focus our thinking, strategies, and actions in new ways that will optimize the use of our resources and accelerate progress against cancer. This challenge also presents new opportunities for the NCI to provide leadership for our Nation's effort to conquer cancer, especially in the development of the new synergies and partnerships needed to achieve this bold vision.

Recent progress across nearly all of biomedical research has set the stage for unimagined progress in biomedicine early in the 21st century. Thanks to research, we now understand that cancer is a disease process—where normal cells are transformed into cancer cells through a series of defined steps that begin with a simple change in the genetic material. If left unchecked, these transformed cells can

progress and spread to cause the suffering and death that we recognize as the horrific burden of cancer. Thankfully, our growing understanding of this process has revealed multiple opportunities to intervene. These new intervention strategies include preventing initiation of the process; detecting it early when it is most amenable to elimination; and arresting the process to stop the spread (metastasis), which is the primary reason that patients suffer unduly and die from their disease. In short, we are rapidly learning how to "preempt" the cancer disease process. We believe in the next few years that new intervention strategies will allow us to prevent and/or eliminate many cancers—and ultimately transform cancer into chronic, manageable diseases that patients live with—not die from.

Scientific advances and major discoveries from areas such as genomics, nanotechnology, proteomics, immunology, and bioinformatics allow us to envision a not too distant future when a patient's genetic, lifestyle, and environmental risk for cancer can be combined with effective prevention and early intervention strategies especially for those at high risk. Serum genomic and proteomic patterns, and advanced imaging technologies, will be employed to detect cancers at the earliest stages. Precise molecular diagnosis and patient-specific prognostic profiling will allow physicians to predict response to specific interventions and provide a rational basis for tailoring therapies. The result will be more efficacious and less toxic, targeted agents delivered to patients. Achieving these outcomes will result in the preemption of a great deal of cancer. I believe that this is no longer a dream but an achievable reality.

To achieve the 2015 challenge we must take the steps necessary to accelerate the pace of progress across the entire cancer research continuum. The basic research which is aimed at discovering the pathways that lead to cancer represents the beginning of a continuum that proceeds through development of new agents and technologies and ultimately to the delivery of these new interventions to patients. Using our ever increasing knowledge of the molecular defects in cancer cells and the biomarkers that define the cancer process will enable the development of the new targeted interventions we need to prevent, detect, and treat cancer.

To achieve this acceleration the NCI has identified six "mission-critical" research areas that we believe will offer significant potential for near term progress against cancer. These include: harnessing the power of the newly emerging science of molecular epidemiology to better identify risk populations; developing an integrative understanding of cancer (systems) biology to discover key biomarkers and targets; facilitating the development of "strategic" cancer interventions for targeted prevention, early detection, and treatment; creating a national integrated clinical trials system to more effectively test these interventions; overcoming health disparities to deliver these advances to those in greatest need; and developing a bioinformatics network to connect the cancer research community and optimize the collection, analysis, and use of the enormous amount of data and knowledge that must be managed and shared.

CANCER BIOMEDICAL INFORMATICS GRID (caBIG)

In this past year's Appropriations Committee Report, NCI was requested to explore ways in which information could be better shared among researchers and cancer care deliverers. In early 2004, the NCI responded by launching an unprecedented program to connect cancer researchers through an advanced technology platform called the Cancer Biomedical Informatics Grid (caBIG). This pilot initiative has the potential to transform the pace of cancer research by providing the tools needed to share information and data. caBIG will be developed by connecting 50 of our NCI-designated cancer centers through an NCI-developed open source system which will in effect become the "World Wide Web" of cancer research. This platform which integrates with the NIH Roadmap informatics initiative will link individual cancer researchers and research institutions across the nation, and around the world, in an open source, federated network that will enable researchers to share tools, standards, data, computing applications, and technologies. This unprecedented bioinformatics system will facilitate the collection, storing, searching, analysis, classification, management, and archiving and retrieval of research data. caBIG will improve the quality of data, provide unimagined access to heretofore limited databases, increase the pace of cancer research and enhance the effectiveness of our investments in cancer research. caBIG has the capability to virtualize cancer research.

caBIG leverages the unique resources and capabilities of NCI's cancer centers to meet the needs of the broad cancer research and care communities. The cancer centers, along with NCI's platforms for translational research, the Specialized Programs of Research Excellence (SPORES), are our partners in this strategic effort to ensure that the fruits of fundamental scientific research can be rapidly captured for

the benefit of cancer patients. This is an example of how the future can be transformed if we can successfully integrate advanced technologies across the discovery, development, and delivery research continuum. In this instance the whole will be a great deal more than the sum of the parts.

NATIONAL ADVANCED BIOMEDICAL TECHNOLOGY INITIATIVE

In developing strategies to optimize progress in NCI's high priority research areas, it became clear that we must proactively identify, develop, and deploy advanced biomedical technologies, such as bioinformatics, across the entire cancer research continuum. This concept represents a critical new element of our overall strategy to achieve the 2015 challenge goal; however, there is clearly a gap between our current level of capabilities in advanced technologies and what is needed. I believe that we now have the opportunity to address this gap through the creation of an unprecedented national advanced biomedical technology initiative that will be transformational for cancer and other diseases.

Achieving our challenge goal will require that we fully integrate advanced "enabling" technologies with the cancer research and care enterprise. Advanced technologies represent those new tools and approaches that enable new approaches to the challenging problems of detecting, controlling, and preventing cancer. Advanced technologies allow cancer researchers to generate, collect, and analyze vast amounts of data, and to pursue innovative approaches that could not be accomplished without these sophisticated tools. As illustrated by our efforts in bioinformatics, the NCI is providing leadership in the development and integration of advanced technologies and we are also building the cross-disciplinary teams needed to implement these new strategies.

Providing advanced technology platforms to scientists working in cancer research is one of our highest priorities at the NCI; and to that end, we have undertaken a cancer-enterprise wide planning effort to develop a national advanced technology initiative for cancer. In planning for this initiative, the NCI has identified (in addition to bioinformatics) multiple areas of advanced technology development that will be crucial in building this national resource. Examples of cross-cutting capabilities, which will support the range of strategic research priorities that we have identified as pivotal areas for progress, include: advanced imaging; biomarkers and proteomics; nanotechnology; and development capabilities such as scale-up for new cancer therapies and prototyping for new diagnostics devices.

We have made significant progress in cancer diagnosis and treatment based on static imaging of the body's organs provided by x-ray, CT, PET, and MRI. The new generation of advanced imaging technologies will target specific molecules and cells. We will be able monitor cellular processes to assess the effectiveness of experimental treatments and to define cancer cells at their earliest stages. Nanotechnology will provide opportunities to develop biosensors that have the capability of detecting changes in cells at the earliest stages of cancer and "report" back on them. This breakthrough technology will also facilitate the design of new technologies to probe cell functions, measure cellular events with unimagined precision, and specifically deliver molecular entities to attack cancer. The combination of advanced imaging and nanotechnology offers the promise of realizing these advances to achieve the exponential progress that is possible at the current inflection point.

The post-genomics era in cancer research has produced vast amounts of information aout the genetic basis of cancer, but perhaps of more importance, we are learning that the functioning of normal and tumor cells is controlled by the proteins that are transcribed from these abnormal genomes. These proteins, along with genes and other indicators of the processes and pathways that distinguish cancer, are called biomarkers. Through the use of advanced technologies NCI is developing innovative strategies to discover and validate biomarkers for use in clinical applications. Biomarkers, along with advanced imaging, nanotechnology, and other advanced technology platforms, will comprise an unprecedented National Advanced Biomedical Technology Initiative for Cancer (NABTIc).

This initiative is a major element of our strategy to achieve NCI's challenge goal to eliminate suffering and death due to cancer by 2015. The NABTIc would leverage and align the capabilities and resources in advanced technology development across the nation—and gain strength from all sectors. Through a network of technology "nodes" it would capitalize on capabilities in our cancer centers and SPORES and optimize the deployment of NCI's existing strengths in advanced technologies that currently exist at our Frederick campus. This initiative is currently being refined and further developed with the aid of our advisors and partners in the extramural community, and a plan to purse this concept is under development.

STRATEGIC PARTNERSHIPS

Finally, to implement many elements of our strategic plan, we will partner broadly With all of the sectors that comprise the cancer community, including other federal agencies and private industry. The NCI is an active partner with many federal agencies, including the Department of Defense, the Veterans Administration, the Centers for Disease Control and Prevention, the Agency on Healthcare Research and Quality, and the Centers for Medicare and Medicaid Services. One partnership that is critically important to optimizing the pace at which laboratory discoveries progress to become new interventions for cancer is our alliance the Food and Drug Administration (FDA). Early last year we created the NCI/FDA Interagency Oncology Task Force to leverage the expertise of both agencies for the expressed purpose of streamlining and accelerating the development of preventive, diagnostic, and therapeutic interventions for cancer. Considerable progress has already been made in the areas of joint training and fellowships, developing markers of clinical benefit, improvement in the overall process of oncology drug development, and creation of a common bioinformatics platform (caBIG) to improve the organization and reporting of data from oncology clinical trials. These partnerships are critical. Each agency, along with the other sectors involved in the development, commercialization, and delivery of the new inventions we desperately need to preempt cancer, is a valued partner who can unite with us to facilitate and speed the overall process.

Last year, I closed by telling members of this committee that we stand at a pivotal crossroads—a defining moment in this nation's effort to prevent and cure cancer. Over the past 12 months we charted the future course forward—through the creation and implementation of innovative strategies—and have undertaken initiatives that will allow us to move rapidly toward a day when cancer will become a chronic disease. What was once a vision is becoming reality through the combined efforts of researchers and leaders from all sectors, patients and their families—and so many others. I believe that together we will realize the economic and human benefits of eliminating the suffering and death due to cancer, and in this quest, inform our efforts to transform our overall health care system.

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 2005 budget of $4,425,507,000 includes an increase of $122,467,000 over the fiscal year 2004 enacted level of $4,303,040,000, comparable for transfers proposed in the President's request.

NIAID conducts and supports research studies to understand, treat, and prevent infectious diseases such as HIV/AIDS and other sexually transmitted infections, influenza, tuberculosis, malaria, and illness from potential agents of bioterrorism. In addition, the Institute supports research on transplantation and immune-related illnesses, including autoimmune disorders, asthma and allergies. For 56 years, NIAID-sponsored research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people worldwide. Historically, NIAID has accomplished its mission with a strong commitment to basic and targeted research in immunology, microbiology, and infectious disease, disciplines that are related and complementary. The new initiatives of the NIH Roadmap, and the information, reagents and infrastructure they will produce, will further promote the efficient and effective movement of NIAID discoveries from the laboratory bench to the bedsides of patients.

THE NIAID RESEARCH RESPONSE TO THE THREAT OF BIOTERRORISM

The use of deadly pathogens such as smallpox or anthrax as agents of bioterrorism is a serious threat to the citizens of our nation and the world, and biodefense research to mitigate this threat is a key focus of NIAID research. Since the anthrax attacks of 2001, NIAID has significantly strengthened, accelerated, and expanded our biodefense research program. NIAID-supported biodefense research includes: (a) basic studies of the structure, ecology, and disease-causing mechanisms of microbes that could be used by bioterrorists; (b) the response of the immune system to these pathogens, and; (c) the translation of this knowledge into safe and effective countermeasures—treatments, diagnostics, and vaccines. To achieve our biodefense research goals, NIAID works closely with partners in academia, industry, and other private and public-sector agencies. Research on potential agents of bioterror prom-

ises to enhance not only our preparedness for bioterrorism, but also for naturally occurring endemic and emerging infectious diseases.

Progress in biodefense research has been swift and substantial. More than 50 major NIAID initiatives involving intramural, academic and industrial partners have been undertaken. As part of this effort, the Institute has greatly increased biodefense research capacity. For example, NIAID recently funded eight Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research. This nationwide network of multidisciplinary academic centers will conduct wide-ranging research on infectious diseases and the development of diagnostics, therapeutics and vaccines. In addition, NIAID is supporting the construction of two National Biocontainment Laboratories (NBLs) and nine Regional Biocontainment Laboratories (RBLs). These high-level biosafety facilities promise to speed the development of effective therapies, vaccines and diagnostics for diseases caused by agents of bioterror as well as for naturally occurring emerging diseases such as SARS and avian influenza.

In addition, NIAID has developed and expanded contracts to screen new drugs; develop new animal models and establish a reagent and specimen repository. NIAID also has made a significant investment in determining the genetic sequences of the genomes of a range of pathogens, which has helped to illuminate the workings of all classes of microorganisms. NIAID-supported researchers and their international colleagues have sequenced genomes representative of all bacteria considered bioterror threats (including multiple strains of the anthrax bacterium), as well as at least one strain of every potential viral and protozoan bioterror pathogen. NIAID also is funding research to better understand the body's own protective mechanisms. A new NIAID program, the Cooperative Centers for Translational Research on Human Immunology and Biodefense, will conduct research to better understand the human immune response to potential agents of bioterror, with the objective of developing new bioterror countermeasures. Another large-scale program is funding sophisticated studies of the human innate system, comprised of the cells that are the "first responders" to infection. Boosting innate immunity holds great promise for developing fast-acting countermeasures to mitigate the effects of bioterror pathogens or toxins.

The ultimate goal of all NIAID biodefense research is the development of medical countermeasures. NIAID-supported scientists have identified: (a) antivirals that may play a role in treating smallpox or the complications of smallpox vaccination; (b) several approaches to blocking the toxins of the anthrax bacterium; as well as (c) antibiotics, antivirals and antitoxins against other major bioterror threats. New and improved vaccines against smallpox, anthrax and other potential agents also are being developed, with the objective of adding them to the Strategic National Stockpile (SNS). For example, NIAID has sponsored the development of a next-generation anthrax vaccine known as rPA, with the goal of adding 75 million doses to the SNS to protect U.S. citizens. Clinical trials of rPA are ongoing; results to date build on similar findings in animal studies and suggest that the vaccine is safe and capable of evoking a robust immune response. Researchers also will test whether the currently recommended course of antibiotic therapy for individuals exposed to anthrax spores can be reduced by vaccinating exposed subjects with rPA.

NIAID-supported researchers also are testing several new smallpox vaccines that may prove at least as effective as the current smallpox vaccine, but with fewer side effects. One of these, modified vaccinia Ankara (MVA), is based on a strain of the vaccinia virus that replicates less robustly than the traditional Dryvax vaccinia virus, and is known to cause fewer side effects than the latter. Human trials of MVA vaccines are underway at NIH and elsewhere. Encouragingly, recent studies by NIAID intramural scientists and their colleagues have shown that MVA protects monkeys and mice from smallpox-like viruses. NIH also has launched the first human trial of a vaccine designed to prevent infection with Ebola virus. The trial vaccine, a type called a DNA vaccine, is similar to other investigational vaccines that hold promise for controlling such diseases as AIDS, influenza, malaria and hepatitis.

HIV/AIDS RESEARCH

Most recent estimates on the scope of the HIV/AIDS pandemic are profoundly sobering. Approximately 40 million people worldwide are living with HIV/AIDS. In 2003 alone, 5 million people worldwide were newly infected with HIV—about 14,000 each day, more than 95 percent of whom live in low and middle income countries. In 2003, 3 million people worldwide with HIV/AIDS died. In the United States, nearly one million people are living with HIV/AIDS, and by the end of 2002, more than 500,000 people with HIV/AIDS had died. As shocking as these numbers are,

they do not begin to adequately reflect the physical and emotional devastation to individuals, families, and communities coping with HIV/AIDS, nor do they capture the huge deleterious impact of HIV/AIDS on the economies and security of nations, and indeed entire regions. Even as the burden of HIV/AIDS continues to grow, recent developments provide some measure of optimism. For example four new antiretroviral drugs were licensed in 2003 by the U.S. Food and Drug Administration (FDA), each of which built on NIAID-sponsored research and/or has been tested in NIAID clinical trials networks. Many other "next-generation" anti-HIV drugs are in clinical trials.

A vaccine that prevents HIV infection—or at least slows the progression of disease—is a critical NIAID priority. Vaccine developers face formidable obstacles, including the genetic diversity of the virus and the lack of a clear understanding of the immune responses that might protect against HIV infection. Nonetheless, NIAID and our academic, industrial, international and philanthropic partners have made significant progress. Numerous HIV vaccine candidates are in various stages of preclinical and clinical development. The new Partnership for AIDS Vaccine Evaluation (PAVE) promises to optimize these efforts. PAVE is a coordinated HIV vaccine research effort that includes the three government agencies most involved in this activity—NIH, the Centers for Disease Control and Prevention (CDC), and the Department of Defense. These agencies will work together to ensure that research protocols, standards, and measures are developed in a coordinated and harmonized manner so that outcomes can be compared across trials in the most cost effective and scientifically efficient manner. International non-government organizations (NGOs) and companies also have expressed interest in joining the partnership. Concurrently, novel approaches to HIV prevention are being studied and validated, including topically applied microbicides that individuals could use to protect themselves from HIV and other sexually transmitted pathogens. As discussed in the new NIAID Strategic Plan for Topical Microbicides, more than 50 candidate agents have shown laboratory activity against HIV and other STDs, and several of these agents have demonstrated safety and efficacy in animal models. In small human studies, several products have proven safe; later this year, NIAID's HIV Prevention Trials Network (HPTN), in conjunction with the National Institute of Child Health and Human Development, will launch a large international study to test two promising products in more than 3,000 women at high risk of acquiring HIV in the United States, five African countries, and India.

RESEARCH ON OTHER EMERGING AND EMERGING INFECTIOUS DISEASES

Infectious diseases have always afflicted humanity, and they will continue to confront us as long as man and microbes co-exist. Unfortunately, the viruses, bacteria, and parasites that cause infectious diseases do not remain static, but continually and dramatically change over time as new pathogens (such as HIV and the SARS coronavirus) emerge and as familiar ones (such as influenza virus and West Nile virus) re-emerge with new properties or in unfamiliar settings.

West Nile virus (WNV) first appeared in the western hemisphere in 1999, and by 2003 had spread to 45 states in the United States. NIAID has moved quickly to address this threat with basic research on the virus and its maintenance in nature, the development of vaccines and treatments, and the provision of reagents and other resources to the research community. NIAID also is supporting the development of three types of vaccines, as well as the screening and testing of WNV therapies. For example, the NIAID-sponsored Collaborative Antiviral Study Group is assessing the safety and efficacy of WNV immunoglobulins in patients with, or at high risk of serious brain diseases caused by WNV.

Severe acute respiratory syndrome (SARS) is a new infectious disease first identified in humans in early 2003. The prompt recognition that SARS is caused by a new type of coronavirus, and the rapid progress in SARS research reflect the dedication of and collaboration by the world's medical researchers and public health experts, including NIAID-sponsored scientists in the United States and abroad. NIAID supports research to understand the epidemiology and biology of the SARS virus and how it spreads, and to develop SARS countermeasures. Several approaches to SARS countermeasures are being pursued by the NIAID Laboratory of Infectious Diseases, the NIAID Vaccine Research Center, and by our contractors and grantees. For example, NIAID is participating in a project to screen up to 100,000 antiviral drugs and other compounds for activity against the SARS virus, and will test the most promising in animal models and human clinical trials. A number of compounds have shown promise in the test tube, including alpha interferon, a drug already approved by the FDA for the treatment of hepatitis B and C infections.

NIAID scientists and grantees are pursuing several parallel approaches in the search for a SARS vaccine. Once these experimental vaccines are ready, NIAID plans to test them in human clinical trials in our network of Vaccine and Treatment Evaluation Units. New research suggests that a SARS vaccine is within reach: NIAID intramural scientists have demonstrated that the mouse immune system develops antibodies capable of single-handedly neutralizing the SARS virus. This discovery affirms that researchers developing vaccines that trigger antibodies to the SARS virus are heading in the right direction. These findings also indicate that drug researchers can use laboratory mice as a model to evaluate whether a drug blocks the SARS virus. Both findings could help lessen the time it takes to develop an effective vaccine or antiviral drugs for SARS.

Influenza is a classic example of a re-emerging disease; it is not a new disease, but it continually changes. Because the replication machinery of the influenza virus is error prone, as the virus multiplies it can mutate to a slightly different form; this is referred to an "antigenic drift." Such viruses might require a slight modification of the yearly influenza vaccine to accommodate these changes. In addition, non-human influenza viruses such as avian influenza, can emerge that may be able to jump species into domestic poultry, farm animals such as pigs, and humans. This type of significant change in the antigenic makeup of the virus is referred to as "antigenic shift." Deadly pandemics associated with antigenic shifts are known to have occurred in 1918, 1957, and 1968. The pandemic that occurred in 1918–1919 after an antigenic shift killed 20–40 million people worldwide, including more than half a million in the United States. This recent history explains the current high level of concern about the appearance of new forms of virulent H5N1 avian influenza viruses in Asia that can adapt themselves by mutation to infect humans as has been the case already in dozens of individuals in Viet Nam and Thailand. Of even greater concern is the possibility that this avian virus can combine or reassort its genes with a human influenza virus and acquire the capability of readily spreading from person to person resulting in a new pandemic. Given the poor condition of public health systems in many underdeveloped regions and the speed of modern air travel, the consequences of such an event, should it result in an influenza pandemic, would be severe.

To address this threat, NIAID supports a broad program to develop more effective approaches to controlling influenza virus infections. Research includes programs to understand the pathogenesis, transmissibility, evolution, epidemiology, and the immune response to influenza viruses, as well as to develop new diagnostics, antiviral drugs and vaccines. NIAID currently supports several research projects to develop vaccines that could be manufactured more rapidly, are more broadly cross-protective, and are more effective than current influenza vaccines. The use of reverse genetics—a tool developed by NIAID grantees—holds the promise for more rapid generation of vaccine candidates that match the anticipated strain expected to circulate during the influenza season. Reverse genetics also can be used to turn highly pathogenic influenza viruses into vaccine candidates more suitable for vaccine manufacturing by removing or modifying certain virulence genes; laboratories around the world are using the technique to prepare vaccine candidates against the H5N1 viruses emerging in Asia. NIAID also is funding the development of new influenza vaccine technologies. Recently, NIAID supported a Phase II clinical trial of a new influenza vaccine produced in a cell culture system as an alternative to manufacturing the vaccine in eggs. Because NIAID has had remarkable success in the past with groundbreaking vaccine research—including advances that led to hepatitis B, *Haemophilus influenzae b,* pneumoccocal pneumonia, and acellular pertussis vaccines—we are confident that one of the approaches that we are pursuing also will lead to a useful, "next-generation" influenza vaccine that can readily be adapted to emerging influenza strains.

RESEARCH ON IMMUNE-MEDIATED DISEASES

Immune-mediated diseases such as autoimmune diseases, allergic diseases, and asthma are important health challenges in the United States and abroad. Autoimmune diseases 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, and the leading cause among children. 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, which has led to the development of many useful therapies. 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. NIAID-sponsored researchers are

now developing novel ways of selectively blocking inappropriate or destructive immune responses, while leaving protective immune responses intact, an area of research known as tolerance induction. In the Immune Tolerance Network, a consortium of basic and clinical scientists, promising studies are underway using tolerance induction to treat autoimmune diseases, such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis; asthma and allergic diseases; and the rejection of transplanted organs, tissues, and cells. So-called "tolerogenic" therapies would replace current lifelong non-specific immunosuppressive regimens (and their often debilitating side-effects) with short-term specific regimens that hold the promise of being curative.

Other important research is being conducted by the recently expanded Autoimmunity Centers of Excellence. The nine centers that make up this program conduct basic research and clinical trials on new immune-based therapies for diseases that collectively afflict between 14 and 22 million Americans. The Institute and our collaborators also have significantly bolstered the study of primary immunodeficiency diseases—disorders caused by inherited flaws in the immune system that increase susceptibility to infections—with funding of the Primary Immunodeficiency Research Consortium (PIRC), a coalition of the world's most prominent researchers in the field of primary immunodeficiency diseases.

Another important NIAID research focus is the development of new interventions to reduce the burden of asthma, a significant and growing public health problem in the United States and many nations worldwide. NIAID has long been at the forefront of discoveries leading to the characterization of asthma and allergic diseases and is now vigorously pursing the translation of basic knowledge into more effective treatment and prevention strategies. To develop interventions to prevent the onset of asthma, more information is needed on the events that induce asthma. NIAID's Inner-City Asthma Consortium (ICAC) will soon launch a large study to define and analyze immunological and environmental influences upon the development of childhood asthma in a cohort of urban children followed from birth.

CONCLUSION

With a strong research base, talented investigators in the United States and abroad, and the availability of powerful new research tools, NIAID anticipates that our basic and applied research programs will provide the countermeasures to improve our defenses against those who would attempt to harm us with bioterrorism, will develop new tools in the fights against HIV/AIDS and other infectious diseases, and will improve therapies and management of immune-mediated diseases.

PREPARED STATEMENT OF DR. NORA D. VOLKOW

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 2005 budget includes $1.019 billion, an increase of $28.273 million over fiscal year 2004 conference level of $990.787 million comparable for transfers proposed in the President's request.

NIDA: 30 YEARS OF DISCOVERY

As the National Institute on Drug Abuse (NIDA) prepares to celebrate its 30th anniversary this year, I am honored to have this opportunity to tell you about some of our remarkable scientific accomplishments and how these advances are setting the course for a better future. A tomorrow that will bring us even better prevention interventions to deter the initial use of drugs by those at risk before they become one of the more than 180 million people around the world who currently abuse illegal drugs. A future that will also bring us better treatment interventions to help those who have already become addicted, and who may suffer from some of the myriad consequences of drug abuse including HIV/AIDS and comorbid mental illnesses. Research supported by NIDA, the world's largest supporter of research on the health aspects of drug abuse and addiction, may even bring us innovative and improved ways to deal with other major health epidemics impacting our society, such as chronic pain and obesity.

ADDICTION AND OBESITY: COMMON NEUROBIOLOGICAL MECHANISMS

Obesity and addiction are serious National health problems that may have much in common. Both addiction and some forms of obesity represent problems resulting from excessive behaviors and lack of impulse control. Knowledge derived from addiction research shows that the brain circuits involved in compulsive eating and im-

pulse regulation are part of the same brain systems involved in addiction, with the neurotransmitter dopamine playing a prominent role. (See Figure 1.) A better understanding of the role of the dopamine and other systems in the motivation for and salience of food may lead us to the development of better medications and behavioral interventions for obesity, as well as addiction. In addition, medications being developed for obesity may also help to reduce drug use. Because of the commonalities between these disorders, we are able to share knowledge of brain and behavior and combine efforts across institutes to forge new insights and approaches that may result in improved health for all. NIDA is pleased to be a key participant in a trans-NIH initiative that is looking at all aspects of this chronic health problem, from its neurobiological underpinnings to helping people establish healthy behaviors.

THE INTEGRATION OF BRAIN, BEHAVIOR AND HEALTH

Understanding the connections between brain, behavior, and health will be critical to improving the health of ALL Americans. Science is at a point where all the elements of the human brain (genes, proteins, circuits) and its development can now be mapped out.

We did it with the Human Genome and I am confident we can do it with the brain. We are already beginning to unravel how various genes, proteins, brain circuits and pathways interact with each other and the environment to affect all aspects of human behavior. This overarching approach is necessary if we are to make progress in improving the quality of life for individuals who suffer from complex disorders, such as drug addiction, which can start at a young age and continue across the lifespan. Now that advances in medical sciences have increased the lifespan of humans, a major challenge becomes to improve the quality of life of individuals, which hinges on our ability to understand the neurobiological underpinnings of human behavior and the impact and malleability the environment can have on it. This pertains not only to problems such as addiction, but other health problems such as obesity, adherence to medical regimens and with establishing and maintaining healthy life styles.

ADOLESCENCE, THE DEVELOPING BRAIN, AND PREVENTION

Collaborating with other Institutes to map out structural and functional aspects of the brain and how it changes throughout development will help us better understand human behavior, and how we can modify it to improve and extend human life. In particular, understanding the developing adolescent brain will be useful in drug abuse prevention efforts. Research indicates that exposure to drugs of abuse in adolescence, when many changes are occurring in the brain, may be a period of significantly increased vulnerability to drugs' effects. Fortunately, advances in science and NIH-funded studies have now brought us to a point where our researchers can use new animal models, new brain imaging technology and other neurobehavioral assessment tools to probe the development of brain and behavior interactions. These new directions in adolescent research will help to inform us on important aspects of cognition, decision-making, emotional regulation, and risk perception during adolescence, and will help us determine how these play a role in the use and consequences of illicit drugs. Armed with new knowledge about how adolescents make decisions, NIDA will be poised to design interventions that can reduce drug experimentation and addiction. We are making progress in this regard through our National Prevention Research Initiative and through our science education activities like "NIDA Goes Back to School Campaign" where science-based materials were disseminated to teachers and students all across America.

EXCELLENT NEWS: DRUG USE DECLINES

Some of the best news to a NIDA Director came in December 2003 when we released the latest data on teen drug use trends. NIDA's long-standing Monitoring the Future Survey showed an approximately 11 percent decline in illicit drug use over the last 2 years by students in the eighth, tenth, and twelfth grades combined. (See Figure 2.) The use of MDMA or Ecstasy decreased by almost fifty percent for the three grades combined in that same time period Also encouraging was the fact that tobacco use among this population was the lowest in the 28 year history of the survey.

NEWS FOR CONCERN: PRESCRIPTION DRUG ABUSE CONTINUES

There was also some disturbing news last year about youth drug use, showing very high rates of abuse of prescription pain killers (e.g., Vicodin® and OxyContin®). Remarkably, 1 in 10 twelfth graders reported abusing Vicodin last

year, making it the second most widely abused illicit substance after marijuana in this population. Hospitals are also seeing more patients coming to emergency rooms for prescription drug abuse. According to data from SAMHSA, between 1994 and 2001 the number of emergency room mentions for hydrocodone and oxycodone increased 131 percent and 352 percent respectively. When used as prescribed, medications like Vicodin can be very effective, but when used improperly they can have very serious adverse health consequences including death from overdose. More research is needed to prevent, educate, and treat prescription drug abuse. Developing new medications that have no abuse or diversion potential is a high priority for NIDA.

Researchers are making progress in this area. Just last year, researchers developed a compound to selectively affect a cannabinoid receptor that is involved in regulating pain. Unlike many other receptors, this one is not found in the brain. When the compound (AM1241) was given to animals, they were less sensitive to several forms of painful stimulation. Not only does this research open up a new arena for pain medication development, but it also sets the stage for developing new medications that are less likely to be abused. Also, NIDA's investment in the development of buprenorphine/naloxone for treating opioid addiction, for example, provides an alternative medication for pain that has less diversion potential than that of other opiate analgesics, and exemplifies how science can help alleviate our Nation's problems.

RESEARCH ON THE CONSEQUENCES OF MARIJUANA, AND THE DEVELOPMENT OF NEW MEDICATIONS

Research continues to shed new light on the deleterious consequences of marijuana, the most abused illegal drug in the United States. Early exposure to marijuana, for example, has been found to increase the likelihood of a lifetime of subsequent drug problems. A recent study, published in the Journal of the American Medical Association of over 300 fraternal and identical twin pairs, who differed on whether or not they used marijuana before the age of 17, found that those who had used marijuana early had elevated rates of other drug use and drug problems later on, compared to their twin who did not use marijuana before age 17. This study reemphasizes the importance of primary prevention by showing us that early drug initiation is associated with increased risk of later drug problems, and it provides more evidence for why preventing marijuana experimentation during adolescence could have a big impact in preventing addiction.

We are also finding that a lifetime of heavy cannabis use can result in an overall dissatisfaction with oneself and with life for most users. Last year, researchers published data on the impact of long-term cannabis use on life achievement such as educational attainment and income. Significantly fewer of the heavy cannabis users completed college and more had household incomes of less than $30,000 compared to individuals who used marijuana minimally.

It is clear, more research is needed to curtail use of this drug. Although the number of marijuana treatment admissions has increased from 92,414 in 1992 to 255,394 in 2001, there are relatively few treatments that have been shown to be effective specifically for marijuana addiction. NIDA is encouraging researchers, as well as the pharmaceutical industry, to become more active in finding new medications for marijuana and for other drugs of abuse. With the fairly recent discovery of an endogenous cannabinoid system with specific receptors and endogenous ligands, the likelihood of finding new targets for medications development is increased. One form of a cannabinoid receptor antagonist (CB1-receptor) has already been developed by several pharmaceutical companies and is undergoing clinical investigation for the treatment of alcoholism and nicotine addition, as well as obesity. Moreover, preliminary data in humans has shown that it can block the effects of marijuana.

ACCELERATING RESEARCH DISCOVERIES BENCH TO BEDSIDE: BEDSIDE TO COMMUNITY NIH ROADMAP AND OTHER INITIATIVES

For science to be useful in preventing and treating addiction this knowledge has to reach the communities. This is an area where NIDA continues to excel. Over the past few years, NIDA has established and strengthened strong collaborative relationships with a number of government agencies, including the Substance Abuse and Mental Health Services Administration (SAMHSA) to build national infrastructures that can facilitate the flow of research into community practice. NIDA's National Drug Abuse Treatment Clinical Trials Network (CTN), which now serves 27 states plus the District of Columbia and Puerto Rico, and the more newly established National Criminal Justice Drug Abuse Treatment Study (CJ-DATS) exemplify

NIDA's commitment to bringing science out of the laboratory and to the community. These initiatives parallel and complement those proposed as part of the NIH Roadmap, including the promotion of interdisciplincary research and the development of improved infrastructures for clinical research, which aim to accelerate the advancement of research discoveries from the bench to the bedside and to the community.

GETTING THE MEDICAL COMMUNITY MORE INVOLVED IN SCREENING AND ADDRESSING HIV/AIDS AND OTHER DRUG ABUSE CONSEQUENCES

Because drug abuse begins in youth and most pediatricians and family physicians typically do not ask questions about drug use, NIDA has launched a Primary Care Outreach Initiative to educate pediatricians and other primary care physicians about the importance of early detection and treatment. The medical community is also being reminded of the need to recognize substance abuse and addiction as disorders that will affect the course of other diseases, including mental illness, cancer, cardiovascular and pulmonary diseases, trauma and infectious diseases. Injection drug use has directly and indirectly accounted for more than one-third (36 percent) of AIDS cases in the United States. Data show that drug abuse treatment can reduce activities related to drug use that increase the risk of getting or transmitting HIV. Also the fact that the health and social consequences of drug abuse, including HIV/AIDS, disproportionately affect racial and ethnic minority populations; for example almost half of HIV/AIDS cases occur in African Americans even though they constitute only 11 percent of the population according to the latest Census data, which highlights the urgency to conduct research that can benefit all populations. (See Figure 3.)

Using our established networks (CTN and CJ-DATS), NIDA is strengthening its commitment to attend to associated health problems like HIV/AIDS, hepatitis and co-morbidity that often accompany substance use. The CTN, for example has a number of treatment protocols underway that address HIV/AIDS and hepatitis. Also, because data suggest that the prevalence of HIV and other infectious diseases is high among drug users in the criminal justice system, with HIV seropositivity rates estimated to be 8–10 times higher than in the general population, NIDA is encouraging more research to prevent and treat the spread of HIV/AIDS and other diseases among individuals in the criminal justice system with substance abuse related problems.

CONCLUSION

Our Nation's investment in drug abuse research is showing reductions in drug abuse rates and its deleterious consequences at the individual, family, and community level. A continued commitment to medical research, and to working with other agencies and sectors, will lead to new advances, technologies and innovations that will result in a healthier population.

Figure 1.

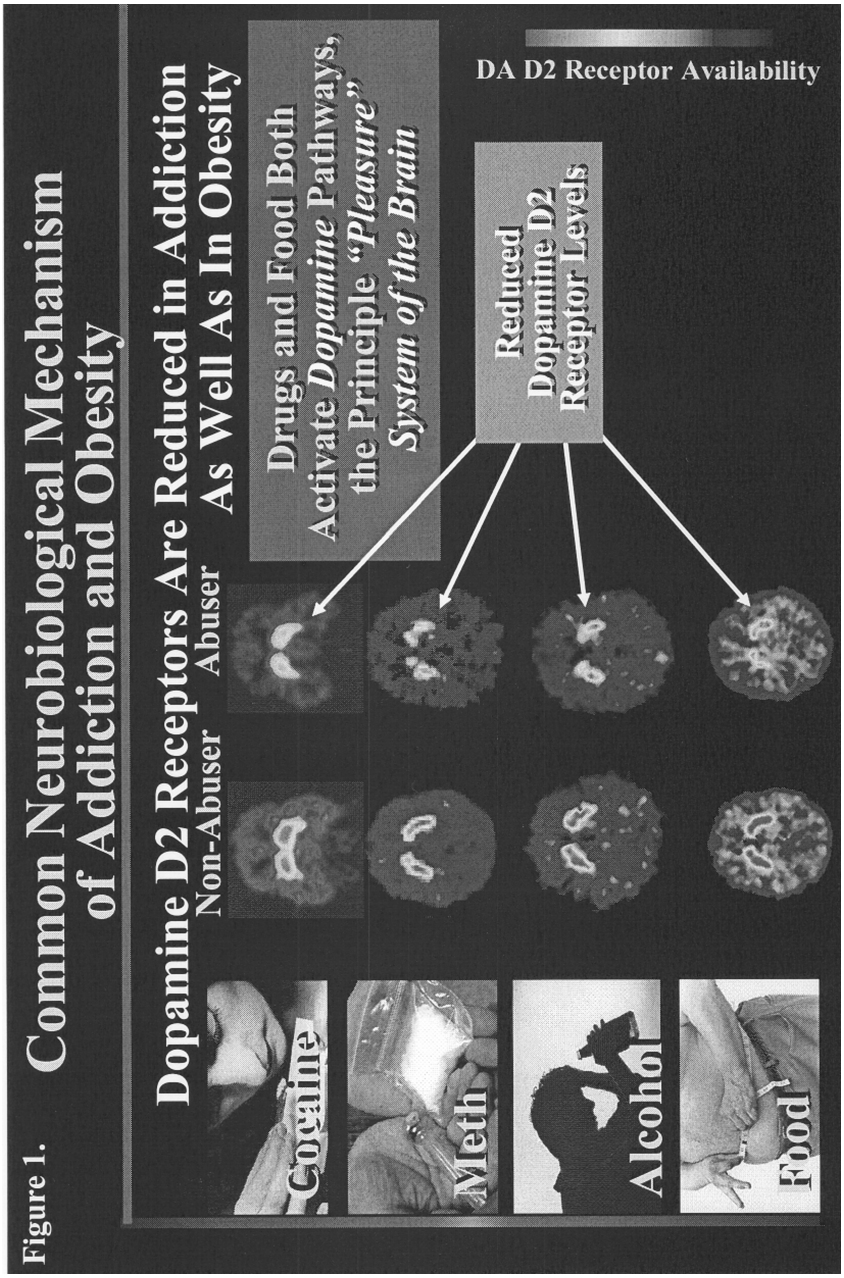

Common Neurobiological Mechanism of Addiction and Obesity
Dopamine D2 Receptors Are Reduced in Addiction As Well As In Obesity
Non-Abuser
Abuser
Drugs and Food Both Activate Dopamine Pathways, the Principle "Pleasure" System of the Brain
Reduced Dopamine D2 Receptor Levels
DA D2 Receptor Availability
Cocaine
Meth
Alcohol
Food

Figure 2.

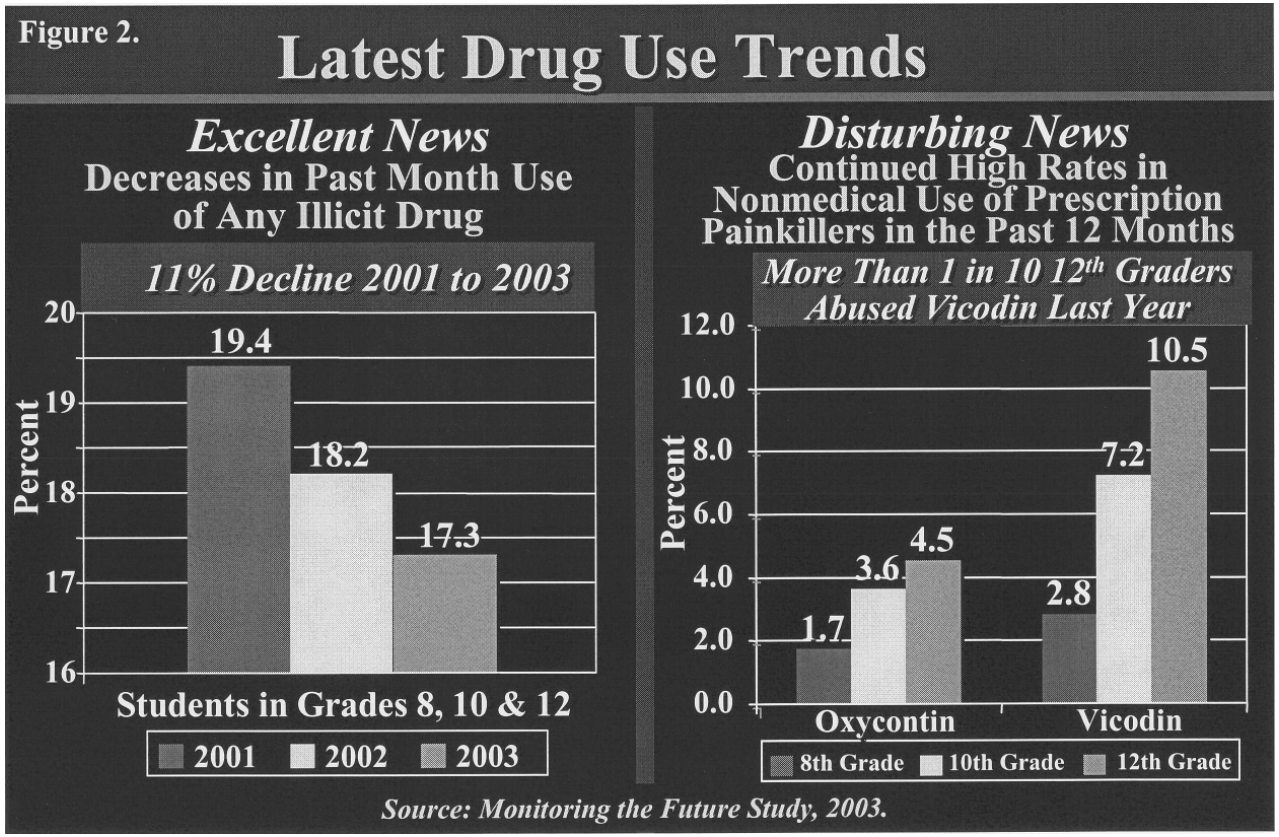
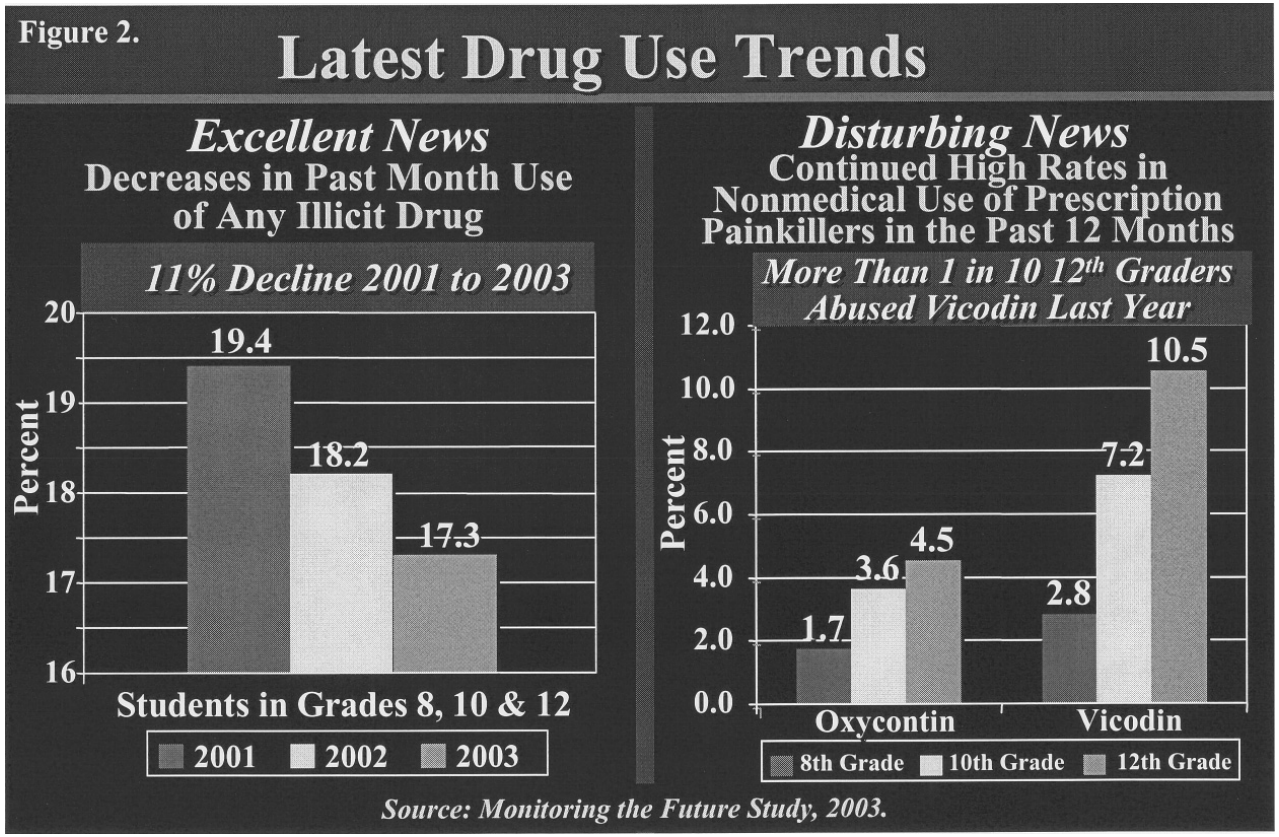

Latest Drug Use Trends
Excellent News
Decreases in Past Month Use of Any Illicit Drug
11% Decline 2001 to 2003
Percent
20
19
18
17
16
19.4
18.2
17.3
Students in Grades 8, 10 & 12
2001
2002
2003
Disturbing News
Continued High Rates in Nonmedical Use of Prescription Painkillers in the Past 12 Months
More Than 1 in 10 12th Graders Abused Vicodin Last Year
Percent
12.0
10.0
8.0
6.0
4.0
2.0
0.0
1.7
3.6
4.5
2.8
7.2
10.5
Oxycontin
Vicodin
8th Grade
10th Grade
12th Grade
Source: Monitoring the Future Study, 2003.

Figure 2.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Source: Monitoring the Future Study, 2003.

PREPARED STATEMENT OF DR. JEREMY M. BERG

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 2005 budget includes a sum of approximately $1,960 million which reflects an increase of $55 million over the fiscal year 2004 enacted level of $1,905 million.

CROSS-CUTTING AND CUTTING-EDGE RESEARCH

Both before joining NIGMS as its new director last November and since then, I have been tremendously impressed by the Institute's leadership in supporting basic biomedical research—that is, scientific studies into the most fundamental biological processes that govern human health. The kinds of research that we fund are both cross-cutting and cutting-edge. NIGMS-supported studies have shed light on everything from the three-dimensional structures of individual proteins—life's building blocks—to the complex interactions between molecules inside cells. More importantly, by uncovering the previously hidden workings of this cellular machinery, not only do we gain a better understanding of the very basis of human health, but we also gain valuable clues to fixing this machinery when it goes awry. Those clues are essential in helping scientists develop better methods to diagnose, treat, and even prevent a wide range of human diseases.

NIGMS has a successful track record of supporting the nation's brightest minds in basic biomedical science. Perhaps the highest recognition of that success can be seen in the number of Nobel Prizes that NIGMS grantees have won over the past four decades: a remarkable 55 to date. This past year was no exception. Roderick MacKinnon, M.D., a biophysicist at the Rockefeller University and a long-time NIGMS grantee, won the 2003 Nobel Prize in chemistry for discovering the structure and function of membrane ion channels—the "gatekeepers" that control what essential molecules move in and out of cells. MacKinnon's breakthrough provides direct visualization of the basis for the electric circuits that are responsible for the functioning of our brains and the beating of our hearts. The detailed structural information is revealing how local anesthetics work and why some drugs have life-threatening cardiac side effects. The work of literally thousands of other researchers has been redirected in response to his discoveries.

NIGMS' impressive return on investment in basic biomedical research is also evidenced by the many other prestigious awards honoring our grantees. In 2003, Rockefeller researcher C. David Allis, Ph.D., won the third annual Wiley Prize in the Biomedical Sciences for his work on chromatin, the complex of DNA with proteins that packages genetic information inside each cell nucleus. The structure of chromatin is largely responsible for why one cell is a nerve cell while another cell is a muscle cell, even though they contain exactly the same DNA sequence. Allis' studies of the chemical modifications that regulate chromatin hold promise for learning how to control genes that suppress and inhibit the growth of tumors in cancer. The previous year, two other NIGMS grantees—Andrew Z. Fire, Ph.D., of the Stanford University School of Medicine, and Craig C. Mello, Ph.D., of the University of Massachusetts Medical School—were among the winners of the second annual Wiley Prize for their groundbreaking discovery of gene silencing by a mechanism called RNA interference. The phenomenon of RNA interference is the subject of upcoming meetings at both the National Academy of Sciences and NIH because of its potential impact for both basic research and for entirely novel approaches to preventing and treating disease.

Even greater advances in biomedical science are possible in the years to come. Through forward-thinking programs designed to foster innovative research and train the next generation of pioneering scientists, NIGMS is playing a leading role in the NIH Roadmap for Medical Research—the exciting new vision of the future recently launched by NIH director Elias Zerhouni, M.D. I would like to share with you some of the key strategies we have developed to help realize this important vision.

BLAZING A TRAIL FOR THE NIH ROADMAP

Throughout its history, NIGMS has helped push back the frontiers of medical knowledge primarily by funding the most promising research grant applications submitted by both new and established scientists. This so-called investigator-initiated research—supported through the NIH's R01 grant mechanism continues to be the most important instrument NIGMS has to promote experimentally based, hypothesis-driven research—the heart of our nation's scientific mission.

In recent years, NIGMS launched a number of larger, targeted initiatives to address both significant opportunities and critical gaps in biomedical research today. In many ways, programs such as NIGMS' Protein Structure Initiative (PSI), its large-scale collaborative "glue grants," and its new Center for Bioinformatics and Computational Biology have blazed a trail for the NIH Roadmap. Today, NIGMS is well positioned to participate with other NIH institutes in transforming the nation's biomedical research capabilities and accelerating the translation of scientific discoveries from the bench to the bedside.

Structural biology is part of the Roadmap's New Pathways to Discovery theme, and NIGMS is playing a key role in this area. One major activity is the PSI, an ambitious 10-year project launched in 2000. The aim of the PSI is to solve the three-dimensional structures of thousands of proteins experimentally and ultimately produce computer-based tools for modeling the 3-D structure of any protein from its genetic spelling, or sequence. Knowing the structures of proteins helps scientists understand how these molecules function in health and disease and aids in the development of new medicines.

Results from the nine pilot centers set up in the first phase of the PSI are promising, demonstrating that automated protein production "factories" are feasible and are yielding high-resolution data that is already being used by scientists around the world. This year, NIGMS plans to ramp up the PSI in its second phase, with the funding of large-scale centers that will dramatically reduce the time and cost of solving protein structures, as well as specialized centers that will tackle challenging problems such as membrane proteins and protein complexes.

NIGMS is also contributing substantially to Roadmap-related initiatives through its support of research aimed at unraveling the complexities of living systems. In 2003, the Institute awarded its fifth glue grant, bringing together a diverse team of scientists to assemble a complete picture of lipids—fats and oils—inside cells, and the role they play in heart disease, arthritis, and other major illnesses. Other ongoing glue grants awarded since the program started in 2000 include projects aimed at understanding cellular signaling and communication, cell movement, and inflammation and the way the body responds to injury.

Last year, NIGMS also added two new Centers of Excellence in Complex Biomedical Systems Research. At these centers, interdisciplinary teams of researchers from both the biological and physical sciences will focus on the emerging field of "systems biology," which seeks to find hidden patterns of biological interactions at all levels, from individual proteins to entire organisms. The new centers join two others launched the previous year with NIGMS funding.

COMPUTER-BASED SOLUTIONS TO BIOMEDICAL CHALLENGES

Harnessing the power of computers to solve complex problems in biology is another major theme in both the NIH Roadmap and NIGMS' research mission. In 2003, the Institute's recently created Center for Bioinformatics and Computational Biology welcomed its first director, Eric Jakobsson, Ph.D., a leading researcher in the field from the University of Illinois at Urbana-Champaign. Dr. Jakobsson has been instrumental in launching one of the first Roadmap initiatives, a program to fund the creation of NIH National Centers for Biomedical Computing. The centers will bring together computer scientists, biomedical researchers, and experts from the experimental, clinical, and behavioral sciences to tackle such challenges as developing computer simulations that will accurately model the complex inner workings of the human brain and other vital systems.

One of the most exciting prospects for computational biology is the promise of turning the vast amounts of data generated by the Human Genome Project into promising new medical treatments that are tailored to the individual. As Allen D. Roses, M.D., senior vice-president of genetics research at GlaxoSmithKline, recently observed, "The vast majority of drugs—more than 90 percent—only work in 30 to 50 percent of the people." NIGMS is addressing this critical issue through the Pharmacogenetics Research Network, a nationwide collaboration of scientists from academia, government, and industry that the Institute spearheaded in 2000, with additional funding from five other NIH institutes. The network has already produced a key computer-based resource that scientists are now actively using: the Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB). With this and other tools at their disposal, scientists will be able to study the effect of genes on people's responses to a wide variety of medicines including antidepressants, chemotherapy, drugs for asthma and heart disease, and many others. The ultimate goal of pharmacogenetics research is to help tailor medicines to people's unique genetic make-ups, thus making medicines safer and more effective for everyone.

Computational biology is also at the heart of another NIGMS initiative: the Models of Infectious Disease Agent Study (MIDAS). An integral component of the overall NIH biodefense plan, MIDAS is a network of scientists who will produce user-friendly computational models for policymakers, public health workers, and other researchers to assist them in making better-informed decisions about emerging infectious diseases. The first centers funded through the MIDAS initiative will launch this year and are expected to contribute significantly to our ability to prevent, detect, and respond to new infectious diseases, either natural or human-made.

Other NIH Roadmap-related initiatives include NIGMS' program to establish high-quality chemical libraries that provide scientists with powerful tools for discovering potential new drugs, and a portfolio of grants designed to stimulate the development of new molecular imaging technologies that can be harnessed to visualize the actions of individual molecules over time in living cells. The effort to create, distribute, and apply these tools will be tremendously enhanced by initiatives that are part of the Roadmap.

TEAM SCIENCE AND INTERDISCIPLINARY TRAINING

The increasingly complex nature of biomedical research today demands new approaches to carrying out the scientific enterprise. NIGMS has been at the forefront of addressing this issue, especially in its support for "team science"—interdisciplinary research that seeks to combine the skills and expertise of scientists from diverse fields and backgrounds. And now as part of another major theme in the NIH Roadmap—Research Teams of the Future—NIGMS is bringing its own experience to the table to help build successful synergies in large-scale research collaborations, and to help prepare the next generation of biomedical scientists trained in multiple disciplines.

For example, NIGMS has led the way in supporting cross-disciplinary research and training through its Medical Scientist Training Program—which leads to the combined M.D.-Ph.D. degree and produces investigators who can bridge the gap between basic and clinical research. Other NIGMS programs support training in the cellular, biochemical, and molecular sciences; systems and integrative biology; the pharmacological sciences; genetics; molecular biophysics; biotechnology; the chemistry-biology interface; and bioinformatics and computational biology.

Many NIGMS research and training programs combine both the biological sciences—cellular and molecular biology, genetics—and the quantitative sciences—physics, chemistry, engineering, mathematics. Indeed, bringing together these two scientific cultures is essential if we are to continue to make important advances in biomedical research in the 21st century. That growing realization has spurred a flurry of activity in recent years. For example, NIGMS joined forces with the National Science Foundation in 2002 to launch an initiative to encourage the use of mathematical tools and approaches to study biology. NIGMS is also partnering with the NIH Office of Science Education on a program to transform undergraduate biology education by incorporating examples and perspectives from the quantitative sciences into biology courses. This program responds to the National Research Council's Bio2010 report.

NIGMS also has a long-standing commitment to increasing the number of underrepresented minorities engaged in biomedical research. Through our Division of Minority Opportunities in Research, NIGMS takes a leading role at NIH to encourage and prepare minority students to pursue training for scientific careers and to enhance the science curricula and faculty research capabilities at institutions with substantial minority enrollments. Both these programs and the efforts to train and recruit more scientists from the physical sciences into biomedical research are essential if we are going to have the biomedical workforce necessary to solve the challenging problems that lead to human disease and drive up the costs of providing health care.

BALANCING LARGE- AND SMALL-SCALE SCIENCE

As promising and worthwhile as these major initiatives are, we must not lose sight of NIGMS' mainstay over the past four decades: investigator-initiated research. By encouraging the best and brightest basic scientists to pursue new directions in their fields, NIGMS has made tremendous contributions to advancing biomedical science. It is often a single investigator, supported by a single grant, who discovers something that turns out to be the tip of a very important iceberg. And we must continue to support these creative minds in order to sow the seeds for tomorrow's advances.

At the same time, we must recognize the need to invest strategically in targeted, larger-scale research to meet the critical needs of ensuring the nation's health and

well-being, its technological competence and competitiveness, and its security. In short, we need to balance small- and large-scale science in a way that both catalyzes and capitalizes on innovation. With our experience in managing thousands of individual research grants every year along with a growing number of multi-institutional, multidisciplinary research efforts, NIGMS can strike that balance while leaving open the door to future directions that are still beyond our powers of prediction.

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

PREPARED STATEMENT OF DR. STORY C. LANDIS

Mr. Chairman and Members of the Committee, I am Story Landis, 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 2005. The fiscal year 2005 budget includes $1,546,623,000, an increase of $44.9 million over the fiscal year 2004 enacted level of $1,500,693,000 comparable for transfers proposed in the President's request.

The mission of the NINDS is to reduce the burden of neurological disorders by finding ways to prevent or to treat these diseases. When I began as Director about six months ago, one of my first priorities was to meet with voluntary groups representing patients and their families. So far, I have met with more than 40 groups, and this remarkable experience has educated me about the extraordinary range of diseases within the NINDS mission, the power of their impact, and the urgency of finding ways to prevent or treat these disorders. These discussions also reinforce the importance of increasing public-private partnerships, which is a goal of our Institute, as well as a major focus of the NIH Roadmap process.

My own research has focused on fundamental questions about how the nervous system develops how genes help wire up connections in the brain, how cells choose to become a particular type, and whether there is any "plasticity" in this process. Issues such as these, long central to basic neuroscience research, are now at the crux of efforts to devise treatments for neurological diseases. I am encouraged by the prevention and treatment strategies emerging from the investment in basic research drugs to home in on the molecules that cause disease, stem cells to repair the damaged nervous system, natural neurotrophic factors to promote survival and growth of brain cells, "vaccines" to prevent stroke, implantable stimulation devices to compensate for brain circuits unbalanced by disease, therapies to turn off, repair or replace defective genes, neural prostheses to read control signals directly from the brain, and behavioral and drug interventions to encourage the "plasticity" of the brain and spinal cord to compensate for damage. The NINDS must continue to support basic research. We must also re-energize our efforts to translate opportunities into practical therapies. Today I will highlight a few of the ways we are working to bring people and resources together to accomplish that.

STEM CELLS

Neural stem cell biology is one area in which basic science and clinical promise are so closely intertwined that it is easy to forget the origins of our understanding of neural stem cells in very basic research. The generation of new neurons in the adult brain was discovered when a basic scientist sought to understand how male canaries learn a new song each spring. This year, NINDS researchers have contributed to advances in identifying and isolating adult neural stem cells, in understanding the signals that control embryonic and adult neural stem cells, and in developing stem cell therapies in animal models that show promise for Parkinson's disease, demyelinating diseases, such as Canavan, Krabbe, or Tay-Sachs, and many other disorders. The NINDS has helped foster research on embryonic and adult stem cells through several initiatives, including training programs in the use of approved human embryonic stem cells, grant supplements to compare these to cells from other sources, and scientific workshops. An NINDS intramural researcher also leads a new NIH facility that is characterizing the approved human embryonic stem cell lines. For the coming year, an initiative targeting collaborative research in stem cell biology, designed to bring together teams of experts from several areas of stem cell biology, is a high priority.

GENES AND THE NERVOUS SYSTEM

Genetics is another neuroscience research area that has made astonishing progress. Overall, researchers have identified more than 200 genes that can cause neurological disorders. Gene findings in the past year are relevant to diseases such

as Parkinson's disease, Charcot-Marie-Tooth disorder, and cerebral cavernous malformations, which can predispose people to strokes. Discoveries such as these lead to improved diagnosis, development of animal models, and the first clues to what underlies disease processes and how to stop them.

Several NINDS efforts bring people and resources together in genetics. Some are simple, but important, such as programs to promote sharing of transgenic mice that are essential models of human diseases. Others are more ambitious, such as the Gene Expression Nervous System Atlas (GENSAT) project, which will map the activity of thousands of genes in the brain and provide genetically engineered mouse strains that allow scientists to study how these genes contribute to health and disease. Microarray screening centers make another new technology and the data arising from it widely available. Microarrays allow scientists to simultaneously monitor the activity of virtually all genes, with wide potential applications to basic and clinical neuroscience; for example, recent studies show micrarrays may predict which patients will respond to approved drugs for multiple sclerosis. The NINDS Human Genetics Resource Center, established this year, makes DNA samples, immortalized cell lines, and accompanying clinical and pedigree data available to all qualified researchers. The repository currently contains samples related to stroke, epilepsy, Parkinson's disease, and motor neuron diseases, including amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA).

TRANSLATIONAL RESEARCH

"Translational research" encompasses the many steps that are needed to move from basic research insights to a therapy that is ready for human testing in clinical trials, and the NINDS has a long history of programs in this arena. For example, over three decades, the Neural Prosthesis program has supported research on electronic and mechanical devices that help compensate for abilities lost through disease or injury, including pioneering research on direct brain control of prostheses, which has recently become a focus of such forward thinking agencies as the Defense Advanced Research Projects Agency (DARPA). The NINDS has responded to increasing opportunities by developing a comprehensive translational research program that fosters cooperative efforts, provides peer review criteria tailored to the needs of translational research, and utilizes milestone driven funding, which is common in industry. In fiscal year 2003, the Institute funded the first projects in this program, focused on gene and stem cell therapies for Parkinson's disease, neuroprotectants for stroke and trauma, treatments for brain tumor, and drugs for epilepsy, ALS and Huntington's disease.

DRUG DEVELOPMENT FOR NEUROLOGICAL DISORDERS

New and expanding efforts to develop drugs complement the broad translational program. The NINDS has awarded a contract for a high throughput screening (HTS) facility, and solicited proposals for the development of disease-related screening tests. HTS uses robotics to rapidly test large numbers of chemicals to find lead compounds for drug development and use as research tools. Ongoing screening efforts focus on ataxia telangiectasia, ALS, and Parkinson's disease. Several NIH institutes are working together to develop chemical libraries focused on the brain, and the NIH Roadmap "Molecular Libraries" component will directly facilitate screening efforts such as these.

Another NINDS drug development effort is a longstanding public-private partnership. Since 1975, the NINDS Anticonvulsant Screening Project has worked with more than 140 companies and 230 academic institutions to test more than 20,000 compounds for anti-convulsant properties, including several drugs now in clinical use. Guided by the epilepsy benchmarks planning process, the Institute is expanding this program with increased focus on preventing the development of epilepsy and on treatment-resistant epilepsy. The NIH Roadmap "Structural Biology" goals to improve our understanding of membrane proteins, such as ion channels that are implicated in some types of epilepsy and neurotransmitter receptors that are often the targets for drugs, will have an important impact on future efforts to develop drugs for this and many other neurological disorders.

Some drugs developed for epilepsy have shown promise for other diseases, such as chronic pain. To take advantage of that kind of crossover, observed in many areas of medicine, the NINDS worked closely with academia and voluntary disease organizations to develop a consortium of 26 laboratories to screen a set of 1,040 known drugs, mostly approved by the U.S. Food and Drug Administration (FDA) for other uses, for potential use against neurodegenerative diseases. The Consortium is sharing data on 29 laboratory screening tests based on molecules, cells in culture, or

simple organisms. Several promising drugs have moved to further testing in animals, and a few may move soon to clinical trials.

PROGRAM TO ACCELERATE THERAPEUTIC DEVELOPMENT FOR SMA

Valproic acid is one example of a drug, now used for the treatment of epilepsy, that in the past year has shown promise in cell culture for a different disease, spinal muscular atrophy (SMA). SMA is the most common single gene cause of infant mortality. In recent years, scientists have discovered the gene defects that cause SMA, developed animal models that mimic essential aspects of the human disease, and devised plausible strategies for developing therapies. Because of the impact of SMA and the state of the science, the NINDS chose this disease as the focus of an innovative approach, initiated in fiscal year 2003, to expedite the development of therapies. The performance-based contract mechanism accelerates all steps from recognition of a research need, through solicitation and review, to funding of targeted research subprojects, with guidance by an expert steering committee that takes a very active role in driving the process. If successful, this approach might be applied to other diseases.

MUSCULAR DYSTROPHY AND CENTERS PROGRAMS

The muscular dystrophies are another group of inherited disorders that are a high priority for NIH. Researchers, beginning more than a decade ago, have identified defects in several genes that can cause the various kinds of muscular dystrophy. These findings have brought improved understanding of what causes these diseases, better animal models to develop therapies, and some practical benefits for example, a new diagnostic test for Duchenne muscular dystrophy will eliminate the need for painful muscle biopsy in many children, and help identify female carriers of the disease before they pass it on to their sons. Therapies to slow or stop muscular dystrophies have been elusive, but there have been encouraging results recently in animals using drugs, stem cells, and gene therapy approaches. To expedite progress against the muscular dystrophies, the NIH has funded three Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, with the expectation that up to three more will be funded competitively in fiscal year 2005. The NIH is also working together with the broadly representative interagency Muscular Dystrophy Coordinating Committee (MDCC) on developing a muscular dystrophy research and education plan for NIH.

The NINDS, often working with other components of NIH, has several centers programs, such as the Morris K. Udall Parkinson's Disease Centers of Excellence, the Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS), the Studies to Advance Autism Research and Treatment (STAART), and the Specialized Neuroscience Research Program (SNRP), which encourages minority scientists and addresses health disparities in neurological disorders. Other centers focus on disorders such as brain tumor, spinal cord injury, and head trauma.

CLINICAL TRIALS

The NINDS continues to set standards of quality and innovation in clinical trials that evaluate whether potential treatments or preventive measures are safe and effective. One recent example, the Neuroprotection Exploratory Trials in PD (NET-PD), was launched in April 2003 to evaluate drug therapies that might slow the progression of Parkinson's disease. The project rigorously selected candidate drugs from a broad array of potential compounds identified by working with clinicians and researchers throughout academia and industry. The 42 clinical sites have recruited individuals with early, untreated Parkinson's, and early phase trials of four drugs will be completed in early 2005. In the coming year, the NINDS clinical trials program is also working to train researchers to conduct clinical trials and to develop a broad clinical trials network that will encompass the greater community of neurologists. Clinical trials for neurological disorders is another area in which the cross-cutting NIH Roadmap efforts for "Re-engineering the Clinical Research Enterprise" are likely to have a major impact.

INTRAMURAL PROGRAMS

Before becoming the director of NINDS, I led the Institute's intramural program on the NIH campus in Bethesda, MD, which is one of the largest basic and clinical neuroscience programs in the world. In addition to recruiting superb individual scientists in fields such as ion channels, genetic diseases of the nervous system, brain tumors, and stroke, a central focus of the program has been to bring researchers together from disparate fields of science. To this end, the Porter Neuroscience Re-

search Center, opening its first phase in 2004, brings together scientists from eight institutes to "put the brain back together" by overcoming artificial disciplinary boundaries within and across institutes and by setting the standard for collaborative research in neuroscience.

FUTURE COOPERATIVE EFFORTS

I have mentioned a few areas in which the NIH Roadmap efforts will facilitate our efforts against neurological diseases, but the same can be said of virtually every major effort within the Roadmap. Driven by the science, several NIH components that have a major focus on the brain are also increasingly working together to form a "blueprint for the brain," in which cooperative efforts across Institutes can expedite progress. These Institutes already cooperate extensively in areas such as training of researchers, genetics, autism, muscular dystrophy, health disparities, brain tumors, stroke, and pediatric neuroimaging, to name a few examples. I hope to report to you in the future about progress in forming other cooperative ventures aimed at our common goal of finding better ways to prevent or to treat all disorders that affect the brain and other parts of the nervous system.

Thank you, and I would be pleased to answer questions.

PREPARED STATEMENT OF DR. STEPHEN E. STRAUS

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2005 budget request for the National Center for Complementary and Alternative Medicine. The fiscal year 2005 budget includes $121.1 million, an increase of $4.2 million over the comparable fiscal year 2004 appropriation of $116.9 million.

INTRODUCTION

Five years ago, recognizing the increasing public health opportunities of complementary and alternative medicine (CAM) and the challenges to research in this area, Congress elevated the NIH Office of Alternative Medicine to the National Center for Complementary and Alternative Medicine (NCCAM). Several months later, as NCCAM's first Director, I articulated a set of priorities for the Center that emphasized growth in the portfolio of rigorous research project grants, enhanced investments in research training and careers awards to build an effective CAM research collective, creation of an intramural research program (IRP), and commitment of stable funding for research centers. As we embark on planning our second 5 years of work, I am pleased to report that NCCAM has achieved these and many other critical objectives.

NCCAM's success to date is evident in some of its vital statistics:

—Under the President's proposed fiscal year 2005 budget, NCCAM's investment in research project grants will have increased from approximately $10 million in 1999 to almost $76 million, while funding for research training and career awards will have increased from under $1 million in 1999 to approximately $8.8 million.

—In collaboration with other NIH Institutes and Centers (ICs), NCCAM has launched nine multi-center Phase III clinical trials of popular CAM interventions for chronic illnesses that affect so many Americans, including osteoarthritis, dementia, cancer, and coronary artery disease.

—NCCAM established an intramural research program in 2001, which studies CAM approaches to diseases of aging, including arthritis, depression, muscle wasting, cancer, pain, and diabetes.

—Based on a comprehensive external review, NCCAM refined its research centers program to support rigorous investigations at both traditionally research-intensive and CAM institutions. In 2003, NCCAM made its first round of revised center awards in three categories: Centers of Excellence for Research on Complementary and Alternative Medicine, Developmental Centers for Research on Complementary and Alternative Medicine, and Planning Grants for International Centers for Research on Complementary and Alternative Medicine. NCCAM's Centers program will foster capacity in CAM research, catalyze more effective and essential partnerships between CAM institutions and research-intensive universities, and facilitate the integration of effective CAM therapies with conventional medical approaches.

Already, the nearly 800 projects that NCCAM has supported since 1999 have yelded over 700 scientific publications, including some that were published in the most prestigious journals—*Journal of the American Medical Association, New Eng-*

land Journal of Medicine, and *Proceedings of the National Academy of Sciences.* Complementing these research and research training activities are extensive efforts to communicate research results and other critical information about CAM to the public and practitioners. NCCAM's award-winning Web site is visited over 1.5 million times each year for its 90 fact sheets, consumer alerts, news releases, and announcements of new research initiatives. In a partnership with the National Library of Medicine, NCCAM helped create a CAM subset on the reference database *PubMed* that now hosts nearly 400,000 reports about CAM studies, which are available to anyone with Internet access. In the aggregate, the investments made in NCCAM's first 5 years are already informing the health care decisions Americans make at home and in consultation with their practitioners.

In its first 5 successful years, NCCAM has become fully integrated within the NIH, developing a research agenda that is responsive to its mission, fiscally accountable, and supportive of rigorous CAM research. NCCAM's research priorities today encompass six thematic areas in which CAM can have a public health impact: obesity, botanicals, brain-body interactions, acupuncture, neurodegenerative diseases, and HIV/AIDS. The next section highlights some of the advances and activities in three of these priority areas.

ADDRESSING THE OBESITY EPIDEMIC

An alarming 65 percent of American adults,[1] 16 percent of adolescents, and 10 percent of American children are now overweight.[2] Obesity results from complex interactions among human biology, behavior, and the environment and, therefore, requires a multidisciplinary approach to prevent and treat it. NCCAM is contributing to the trans-NIH strategy to address this epidemic by supporting studies of the safety and efficacy of popular, but unsubstantiated, dietary approaches to obesity and its many complications. One of the most popular approaches today is the diet plan championed by the late Dr. Robert Atkins, which emphasizes a low-carbohydrate, high-fat, high-protein regimen.

In fiscal year 2003, NCCAM-sponsored researchers reported in the *New England Journal of Medicine* on a ground breaking 1-year, multi-center trial about the effects of the Atkins diet on weight loss and risk factors for cardiovascular disease. At 6 months, those on the low-carbohydrate diet had lost more weight and had reduced levels of blood lipids more than those on the conventional diet. At the end of 1 year, however, the differences between the two groups of dieters lessened, leading investigators to call for larger and longer-term studies. NCCAM is working with its NIH partners to support a larger and more definitive study.

In its intramural program, NCCAM researchers are testing whether the dietary supplement glucosamine, used by over 4 percent of older Americans for degenerative arthritis, causes resistance to insulin, a condition that predisposes one to diabetes—a disease linked to obesity. Other IRP studies are evaluating carnitine, a nutrient essential for the normal metabolism of fats, to see whether it can reduce abdominal fat content, stimulate weight loss, and improve glucose utilization.

In fiscal year 2005, as part of the overall trans-NIH focus on obesity, NCCAM will cosponsor two major initiatives in obesity research, *Neurobehavioral Basis of Obesity* and *Prevention and Treatment of Pediatric Obesity in Primary Care Settings.* The first seeks to bridge the gap between understanding the molecular and genetic regulation of food intake and behavioral influences on obesity. The pediatric initiative will evaluate preventive and therapeutic strategies for obesity that could be recommended for children and adolescents in primary care settings, such as a physician's office, primary care clinic, or HMO.

EXAMINING THE SAFETY AND EFFECTIVENESS OF BOTANICAL PRODUCTS

Approximately 14 percent of Americans use herbal supplements to prevent disease, maintain wellness, or treat illness or pain.[3] Many of these people also take prescription drugs. NCCAM-supported research is identifying herbal products that interact with drugs and the underlying biochemical mechanisms of these interactions. For example, studies have shown how St. John's wort and PC SPES (a botanical mixture that had been used to treat advanced prostate cancer) induce the

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[1] *Journal of the American Medical Association,* 288 (14): 1723–1727, Flegal *et al*, "Prevalence and trends in obesity among U.S. adults, 1999–2000"

[2] *Journal of the American Medical Association,* 288 (14): 1728–1732, Ogden *et al*, "Prevalence and trends in overweight among U.S. children and adolescents, 1999–2000"

[3] *Journal of the American Medical Association,* 287 (3); 337–344; Kaufman *et al.,* "Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey."

activity of a key liver enzyme that is responsible for the metabolism of some 80 percent of all drugs. This finding shows how herbal supplements have the potential to either enhance a drug's toxicity or reduce a drug's effectiveness when a patient takes both dietary supplements and prescription medication.

Each year in the United States, an estimated 70,000 people are diagnosed with head and neck cancers, which are typically resistant to multi-drug chemotherapy. In fiscal year 2003, NCCAM-sponsored researchers examined extracts from the root of *Scutellaria baicalensis*, a Chinese herb, for activity against head and neck cancers. The new study is promising because it shows that the herbal extracts strongly inhibit the growth of human head and neck cancer cells *in vitro* as well as in mice with tumors composed of human cells. Future studies will determine the herb's effects on regulating the cell replication cycle and whether it can be translated into a safe and effective intervention for head and neck cancer patients.

While some research studies confirmed the promise of certain botanicals, others have found herbs that do not deliver on their claims. One example is guggulipid, a botanical extracted from the resin of the mukul myrrh tree, that is marketed in the United States as a dietary supplement to help control blood cholesterol levels and maintain a "healthy heart." In an 8-week placebo-controlled study involving over 100 subjects, NCCAM-funded scientists found that neither the standard or even higher doses of guggulipid significantly lowered the levels of the key low-density lipoprotein (LDL) form of cholesterol in people with high blood cholesterol. This study highlights the need to study popular botanicals that the public is using so that individuals can make informed decisions regarding their own care.

In fiscal year 2005, NCCAM will co-sponsor three important initiatives on the use of botanicals as dietary supplements. Through a newly refined Botanical Research Centers Program being mounted with the NIH Office of Dietary Supplements and the National Institute of Environmental Health Sciences, NCCAM will support interdisciplinary studies of botanicals to generate evidence regarding their safety and potential public health benefits. NCCAM also plans to establish a Phase I Resource Center (PRC) to define the pharmacology and optimal dosing of botanical products and functional foods. Finally, in fiscal year 2005, NCCAM plans to initiate *in vitro*, animal, and preliminary clinical studies of *Silybum marianum* (milk thistle) and its derivative silymarin as a treatment for chronic hepatitis and cirrhosis of the liver, conditions that affect millions of Americans for whom, to date, there is no effective treatment.

Through these programs, NCCAM thoughtfully is investing in programs of basic research to discover natural products and food supplements that could open new avenues for prevention and treatment of conditions that affect the health, well being, productivity, and quality of life of millions of Americans.

INVESTIGATING BRAIN-BODY INTERACTIONS

NCCAM scientists are exploring ancient practices such as meditation, Tai Chi, hypnosis, and yoga to understand their abilities to harness the healing effects of the mind on the body. For example, NCCAM grantees are conducting pilot studies of yoga as a behavioral intervention for the management of chronic obstructive lung disease, insomnia, and chronic low back pain, as well as investigating whether one's spirituality and religiosity have a significant influence on immune system functioning.

In 2003, NCCAM-funded researchers reported that a traditional Chinese meditative exercise regimen, Tai Chi, could enhance physical performance and immune responses in older people. As people age, immunity to the virus that causes chicken pox wanes until the infection can reactivate from its dormant state in nerves and develop into the painful condition shingles. The study concluded that older adults who participated in a form of Tai Chi for 15 weeks experienced statistically significant increases both in ellular immune responses to the virus and in physical performance. This is the first scientific study to show that a CAM approach is responsible both for improvements in physical function and in virus-specific immunity and provides the basis for a larger study of Tai Chi currently being supported by NIH.

To further stimulate research in the field of brain-body interactions, NCCAM is a cosponsor of several NIH research initiatives. The first effort, entitled *Mind-Body Interactions and Health: Exploratory/Developmental Research Program*, will foster program development at institutions that have high potential for advancing mind-body and health research. The second initiative, *Research on Mind-Body Interactions and Health*, will support interdisciplinary collaborations and innovations to understanding the underlying processes of mind-body interactions and health and translating basic knowledge into interventions and clinical practices.

LOOKING FORWARD

Five years ago, the discipline of rigorous CAM research was in its infancy. Absent precedents for the field, NCCAM's initial efforts led to supporting an array of studies spanning numerous CAM practices and health conditions. In these first years, NCCAM found that to better ensure that its funds yield compelling results, it needed to encourage studies on mechanisms of action of CAM approaches, well-developed Phase I and II clinical trials as a foundation for future definitive studies, and collaborations between CAM and research-intensive institutions. In the coming years, the Center will refine its research priorities even more, to emphasize those areas and conditions for which CAM can have the greatest health impact. To this end, in 2004, NCCAM began a formal process to seek input from its many stakeholders, including the scientific community, health professionals, and the public to further target its research, training, and communication goals and to craft a long-term plan to guide the way toward its tenth anniversary.

Complementing this strategic planning process are the trans-NIH Roadmap for Medical Research activities in which NCCAM leadership has a significant role. Core themes of the Roadmap resonate strongly with NCCAM because they promise to provide NCCAM grantees access to more sensitive technologies, richer environments for learning and conducting interdisciplinary research, and a re-engineered platform for clinical trials, all in ways that small institutes and centers could never achieve on their own.

In the coming months and years, I look forward to sharing with members of the Committee, the scientific community, practitioners, and the public our second strategic plan and the results of the research and training investments that we have made. Thank you for your interest in NCCAM's progress and plans. I would be pleased to answer any of your questions.

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 2005 budget is $650,027,000, an increase of $18,964,000 over the comparable fiscal year 2004 appropriation.

INTRODUCTION

Most complex diseases arise from the interplay between biology, environment and behavior. It is the NIEHS' mission to understand this interplay as it translates into increased disease risk. Thanks to the rare confluence of technology breakthroughs in analysis of genes and proteins and their recent application to the environmental health sciences, gene-environment interactions can now be investigated with more rigor and specificity. Our new opportunities within the framework of the NIH Roadmap also offer promise for a more rapid understanding and translation of this knowledge into improved public health. I will outline several of the NIEHS' most important efforts.

GENES AND ENVIRONMENT

There are two principal avenues for exploration of the complex interplay between genes and environment. One is to look at the variations of genes themselves, and the other is to examine how genes respond to environmental stressors. In the case of the first approach, NIEHS is conducting the Environmental Genome Project (EGP) an effort to resequence 544 "environmentally responsive" genes—genes which are thought to be involved in an individual's susceptibility to environmental exposures—and to identify alleles or genetic variants associated with these genes. The key objective of the EGP is to discover and characterize these alleles or genetic variants, called polymorphisms, and to define their roles in the pathways by which environmental agents exert their effects on human health and disease.

Last April, the EGP completed the first phase, publishing a catalog of variation in over 200 genes responsible for detoxifying environmental compounds such as pesticides, as well as metabolizing natural biological components such as hormones. Over 17,000 single nucleotide polymorphisms (SNPs) were identified, with more than 1,000 in coding sequences. This information is already being used to make significant scientific discoveries. For example, it was found that people suffering from benzene-induced leukemia lack a certain SNP in the gene responsible for utilizing a vitamin B, folate, that healthy people have. Thus, the ability to metabolize folate might relate to the relative risk of developing leukemia among benzene workers.

To aid in the functional characterization of SNPs in both coding and regulatory sequences of specific genes, NIEHS initiated the Mouse Genetic Variation Mapping Initiative. The mouse is the most widely used mammalian model system for the study of human health and disease for several reasons, including the fact that the genomes of mice and other mammals are highly conserved. Most human genes have counterparts in the mouse genome; thus, cloning of a gene in one species often leads to cloning of the corresponding gene in the other. The mouse also offers well developed toxicological and pathology databases and molecular genetic techniques for construction of gene knockout strains. Data generated using rodent models have been used widely in preparation of environmental regulatory policy and by the pharmaceutical industry.

One of the greatest challenges for comparative toxicogenomics is the integration of the vast amount of genomic information being generated for a variety of model organisms. At present, there are several disparate but complementary databases on genomic sequences. Most of these databases provide data on gene and genome sequences for individual animal species. These databases do not provide a means to link the genome data to specific environmental chemicals or to toxicological and biological endpoints. They also do not enable researchers to compare information about potentially similar genes and biological responses across multiple species.

Integrating the large number of disparate data sets is the goal of the Comparative Toxicogenomics Database (CTD). The CTD was developed through a collaboration of five NIEHS-funded Marine and Freshwater Biomedical Sciences Centers. The goal of the CTD is to develop a comparative database that links sequence information for genes that are relevant to toxicology to information about gene expression, toxicology and biological processes. The primary focus of the CTD is on marine and aquatic organisms as model systems for human diseases. The initial focus is also on genes that have been identified through the NIEHS' EGP as important for toxicology in these model systems. However, the database will eventually merge all gene sequence information generated on all vertebrates and invertebrates, including aquatic organisms, worms, flies, rodents, and people. The CTD provides information about gene curation and annotation (gene synonyms, sets and functions) and links between gene sequence and toxicity data published in the scientific literature. These aspects of the database represent an important advancement for comparative toxicogenomics. Understanding these mechanisms will allow more informed assessment of human risk by extrapolating toxicity data from animal models to people and will provide a mechanism by which members of the research community can share their data and promote fruitful avenues for future toxicological research.

At present, the CTD is the only fully curated, publicly available database of its kind in the world. However, it serves as a prototype database and data resource for more comprehensive efforts ongoing at the NIEHS. The centerpiece for these discoveries is the NIEHS' National Center for Toxicogenomics (NCT), which uses a multidisciplinary approach to identify genes and proteins affected by specific environmental exposures. When a person is exposed to a chemical, physical, or biological agent, cells in the body may respond by switching on some genes and switching off others, potentially changing the proteins that are produced by the cells. The on/off pattern of various genes is different for each specific exposure, creating a characteristic pattern or "signature," which scientists hope will be useful in classifying chemicals by their effects on various cellular processes. By constructing and populating a database of chemical effects on biological systems, the NCT is assisting the field of environmental health research to evolve into an information science in which gene and protein expression datasets are compiled and made readily available to the scientific community. By building on the data infrastructure being developed through the CTD and other databases, NIEHS scientists are developing the sequence-driven and context-documents Chemical Effects in Biological Systems (CEBS) knowledge base. CEBS is planned as a public toxicogenomics knowledge base that combines and integrates scientific data from a multitude of public domain data sources. These data sources include studies of genetic polymorphisms, gene expression and proteomics, metabolism and toxicology. Once sufficient high quality data have been accumulated and assimilated, it will become possible to characterize an unknown environmental exposure by comparing its gene and/or protein expression profile to compendia of expression profiles in the database. Ultimately, the NCT will develop the capacity to use gene expression signatures and other data to facilitate characterization of toxicants and their biological effects. Through the predictive capabilities expected from toxicogenomics, adverse toxicity in clinical trials will be reduced and the efficiency of bringing new therapeutics to the public will be increased; adverse effects from long-term use or from combinations of therapeutic agents will be better understood and reduced. The final payoff for investing in CTD and CEBS will be more rational environmental health policy and an improved un-

derstanding of gene-environment contributions to the major causes of human death and disease.

OBESITY AND ENVIRONMENT

Environment and behavior intersect in fundamental ways, intersecting with our biology but also with each other. In no area of public health is this more apparent than with the problem of obesity. There is a growing body of literature that illustrates the negative physical and mental health effects of unregulated and poor urban, rural, and suburban development and planning. These studies have documented increased rates of obesity, diabetes, depression, anxiety, and heart disease in these poorly developed areas. For example, in sprawling communities, higher dependence on motor vehicles has resulted in polluting the atmosphere with ground-level ozone and particulate matter, contributing to human health problems such as lung and cardiovascular disease. People most affected by air pollution include older adults with pre-existing diseases; children, especially those with asthma; persons with inadequate health care; and even healthy individuals who work and exercise outdoors. Lack of safe sidewalks in growing urban areas has resulted in a reduction in the number of children walking or biking to schools. Today, only 10 percent of children walk or bicycle to school—a 40 percent reduction over the last 20 years (according to researchers in *Urban Land*). Research suggests that inadequate urban planning, such as a lack of bike paths and sidewalks, results in a more sedentary lifestyle of children, which, in turn, may be a factor in the growing rates of childhood obesity. All of these examples demonstrate how the physical or built environment influences choices that ultimately affect health.

The NIEHS is designing a program as part of the trans-NIH obesity initiative which is designed to examine how the built environment affects obesity and the effectiveness of changes in community planning, design, and development in reducing the extent of obesity and associated comorbidities. These intervention research projects will develop tools to characterize and measure individual and population-level indicators of healthful communities—and of residents' lifestyles and behaviors—that prevent or reduce obesity. We hope that not only will studies of interaction between parameters of the built environment and individual lifestyle choices and behaviors help delineate factors that can prevent or reduce obesity, but also that this work will point the way towards new, cost-effective intervention strategies that promote healthful environments and behaviors.

In a related initiative, NIEHS is partnering with the Robert Wood Johnson Foundation to support a program called Active Living by Design, which will provide support to 25 communities across the country to implement active living programs, policies, and communication strategies to improve community development and promote more healthy lifestyles. The NIEHS is providing an evaluation component to the program to determine the efficacy of various policies and promotions in reducing obesity.

It is critical to delineate the role and impact of community design, planning, and development on individual and population health by understanding the contribution of urban/rural planning (i.e., land use decisions), housing structure, transportation issues, and the availability of public and green spaces as determinants of mental health, physical activity, nutrition, and access to healthy foods. In turn, modifying such parameters may reduce the prevalence of obesity in adults and children. This research effort will require integrated, interdisciplinary research teams, including biomedical scientists, behavioral scientists, social scientists, clinicians, epidemiologists, urban planners, developers, and architects, as well as active participation of community members. It is expected that such research will result in a greater understanding of the health benefits of living in communities that promote healthful environments and behaviors and may also impact policy for land use and public health.

TOXICOLOGICAL EVALUATION OF NANOSCALE MATERIALS

Nanoscale materials are a broadly defined set of substances where at least one critical dimension is less than 100 nm. Ultrafine particulate matter, e.g. the very smallest particles of soot from such sources as diesel exhaust, is a well-known example of ambient nanoparticles; however, this initiative will initially focus on manufactured nanomaterials of current or projected commercial importance. Nanoscale materials can in theory be engineered from nearly any chemical substance; semiconductor nanocrystals, organic dendrimers, and carbon fullerenes and carbon nanotubes are a few of the many examples. Nanoscale materials are already appearing in commerce as industrial and consumer products and as novel drug delivery

formulations. Commercial applications and resultant opportunities for human exposure may differ substantially for nanoscale vs. "bulk" materials.

Currently there is very little research focus on the toxicology of manufactured nanomaterials. Studies from the ultrafine particle inhalation toxicology literature hint at the complexity of the topic and suggest that nanoparticle size can impact toxicity equally if not more so than chemical composition. There are indications in the literature that manufactured nanomaterials may distribute in the body in unpredictable ways and that certain nanoparticles have been observed to preferentially accumulate in particular organelles. Surface properties can be changed by coating nanoparticles with different materials, but surface chemistry also is influenced by the size of the particle. This interaction of surface area and particle composition in eliciting biological responses adds an extra dimension of complexity in evaluating potential adverse events that may result from exposure to these materials.

The National Toxicology Program (NTP) is developing a broad-based research program to address potential human health hazards associated with the manufacture and use of nanoscale materials. The intent of the NTP/NIEHS research program is to evaluate the toxicological properties of major nanomaterials classes which represent a cross-section of composition, size, surface coatings, and physico-chemical properties, and use these as model systems to investigate fundamental questions concerning if and how nanomaterials can interact with biological systems. Some of these fundamental questions include: What are the appropriate methods for detection and quantification of nanoscale particles in tissues? How are nanoparticles absorbed, distributed in the body and taken up by cells? Are there novel toxicological interactions?

Discussion and review of efforts in this area has highlighted the need for studies of nanoscale materials that not only apply existing toxicology testing methodologies, but also explore the development of appropriate novel toxicological methods to adequately assess potential human health effects. The NIEHS is looking ahead to be able to supplement our critically inadequate knowledge of this rapidly emerging technology.

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 2005, a sum of $1,421 million, which reflects an increase of $39 million over the comparable fiscal year 2004 appropriation.

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 describe some of our efforts, in collaboration with trans-NIH initiatives, to bring new treatments from the laboratory to the clinical research arena and ultimately to widespread practice in the community.

BURDEN OF MENTAL ILLNESS

The National Institute of Mental Health faces an enormous challenge: to reduce the burden of mental and behavioral disorders through research on mind, brain, and behavior. Mental disorders are real illnesses that can be diagnosed and in many cases, treated effectively. The need is vast: 450 million people worldwide suffer from a mental disorder. Mental illnesses account for four of the top six causes of disability among 15–44 year olds in the Western world. By 2020, psychiatric and neurological conditions will have likely increased their share of the total global burden by almost half, from 10.5 percent to 15 percent.

In addition to morbidity, mental illnesses are a substantial source of mortality. Of the 30,000 Americans who die by suicide each year, 90 percent have a mental illness. Deaths from suicide outnumber deaths from homicide (18,000) as well as deaths from AIDS and most forms of cancer. Suicide is high among several ethnic minority groups, though remains highest in older white males. Between 1952 and 1992, the incidence of suicide among adolescents and young adults nearly tripled; currently it is the third leading cause of death in adolescents.

In addition to the emotional costs, the economic costs of mental illness are staggering. According to the recent report from the President's New Freedom Commission on Mental Health, the cost in the United States from both direct (treatment-related) and indirect (productivity loss) expenses may exceed $150 billion per year with rapid annual increases, especially in the drug treatment area. Adding to that, more than three million people are receiving disability benefits due to mental disorders. They constitute nearly 28 percent of disabled workers in the Social Security

Disability Insurance Program, and more than 35 percent of people with disabilities receiving Supplemental Security Income. Together they accounted for an estimated $25 billion dollars in cash benefits in 2001.

SCIENCE TO SERVICE

For many mental disorders, there is some form of treatment, but there is no cure. The report from the President's New Freedom Commission on Mental Health describes the need for transforming the delivery of evidence-based treatment and services to communities where they can directly benefit people with mental illness. To achieve this goal, NIMH recognizes the need for the research enterprise to partner with other organizations such as the Substance Abuse and Mental Health Services Administration (SAMHSA), state governments, and advocacy groups. In one such example, NIMH and SAMHSA recently funded nine one-year grants to state mental health agencies to support planning activities toward the implementation of evidence-based practices. Proposed science to service research activities include devising evidence-based group-focused activities for specific ages (child, adult); managing medication for those with schizophrenia; and providing cognitive behavioral therapy for people with depression. Each grant is expected to result in future research and service development initiatives. Translating scientific breakthroughs into far-ranging clinical care, we believe, is an urgent and achievable task.

PROGRESS IN GENETICS

In addition to applying what we already know, we must continue the scientific efforts required to develop better treatments to bring us closer to our ultimate goals of curing or preventing severe mental health disorders. To attain these ambitious goals, we will need a much larger variety of medications and behavioral therapies than are currently available—treatments that can be tailored to work for all those who need them, not just a small subset. As an initial first step, we must discover how genes and the environment interact to produce the biological variations that can signal vulnerability to disease. This year has been remarkable in its wealth of discoveries of genes as well as gene-environment interactions. In depression, for example, NIH-sponsored researchers found that a variation in the gene that regulates serotonin transmission can make a person more vulnerable to depression when faced with stressful life experiences. Those without the gene variation had no such vulnerability, and appeared to be resilient even in the face of many life stresses. Those with the gene variation were not depressed until and unless they faced major life stressors. This suggests that some of the environmental contributors to illness may only be detected by first identifying variations in genetic risk. Future research could help us apply this information to identify those most at risk, and develop treatments that either target genes or the environment, or both. It also suggests a new model with which to test genetic vulnerability and environmental stresses in other major diseases, such as schizophrenia, anxiety disorders, or eating disorders.

This year we have also seen exceptional progress in research on schizophrenia. Several genes have been found which appear to significantly contribute to the development of schizophrenia, providing at least a partial blueprint for the genetic risk architecture of the disease. While we still need to learn more about how they work, this group of genes should bring us closer to diagnostic tests for early detection, new targets for treatment, and even new strategies for prevention. In other studies, genes have been found which are thought to play a role in obsessive-compulsive disorder, panic disorder, and autism. NIMH researchers have also identified genes involved in memory and information processing, both of which are impaired in schizophrenia and various other disorders. These studies were among those named collectively as the number two scientific "breakthrough of the year" by the prestigious journal Science in December. Most of the studies listed were conducted by intramural or NIMH-funded investigators. Studies this year have also provided new insight into the neural circuitry of anxiety and fear processing, suggesting new targets for drug development to treat anxiety, post-traumatic stress disorder, and various phobia disorders.

SCHIZOPHRENIA TREATMENT INITIATIVE

While the news on schizophrenia has been exciting, we recognize that the road from gene discovery to prevention and treatment is neither simple nor rapid. To accelerate this process, we created a new initiative on schizophrenia research. A primary component is a new intramural interdisciplinary team, ranging from molecular to clinical scientists, who will lead a broad effort to understand how different gene variations alter neural networks and disrupt brain activity, leading to cognitive impairment and psychosis. The team will work to identify the role of these

vulnerability genes, including their individual contributions to risk, severity of the disease, and drug response.

A second component of the initiative is a program that targets cognitive problems for people with schizophrenia. Cognitive deficits, such as trouble with memory, attention, and executive function (capacity to make judgments and control impulses) are major determinants and predictors of long-term disability in schizophrenia. They remain a significant barrier to a productive life for people with the disease, yet the medications currently available provide no relief for cognitive problems. There has been a lack of scientific consensus on which cognitive impairments should be targeted and which tools are best for measuring them. As a result, the FDA has not been able to recognize cognition in schizophrenia as a valid treatment endpoint for drug registration. To address these issues, NIMH launched the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program. It brings together representatives from academia, industry, and regulatory agencies to develop a comprehensive assessment tool to measure cognitive functioning in people with schizophrenia. The second phase is to develop and test novel compounds designed to enhance cognition.

ROADMAP

For most of our recent genetic discoveries, we lack the molecular tools needed to link the genes to new treatments. The search for new molecular tools for schizophrenia and other mental disorders will be aided greatly by one of the NIH Roadmap initiatives that will establish a repository of diverse organic chemicals. Organic chemicals, commonly referred to as "small molecules," have proven to be extremely important to researchers exploring the functions of the cell at the molecular level. In fact, most medicines, from aspirin to antihistamines, are small molecule compounds. This new "molecular library" will offer researchers access to hundreds of thousands of small organic molecules that can be used as chemical probes to study cellular pathways. These compounds will help validate new targets for drug therapy more rapidly, and will enable other researchers to move them into the drug-development pipeline.

AUTISM

NIMH plays a major role in a broad-based NIH effort to create a network of autism research centers focusing on the biomedical and behavioral aspects of the disease. Five institutes at NIH are coordinating their research efforts in an initiative called the Studies to Advance Autism Research and Treatment (STAART) Centers program. This year, the institutes awarded grants to support six new autism research centers, in addition to the two that were funded last year. NIH expects to spend $65 million over five years for the eight centers.

NIMH is the lead agency for the Interagency Autism Coordinating Committee (IACC), a group charged with coordinating research and other efforts on autism within the Department of Health and Human Services (HHS). NIMH took the lead in organizing the "Autism Summit Conference: Developing a National Agenda," a joint effort of the HHS and the Department of Education, held in November 2003. About 650 people attended the meeting to address three major areas of emphasis: biomedical research, implementing early screening and diagnosis, and improving the accessibility and coordination of services. A key focus of the meeting was the introduction of a 10-year national research agenda, developed by an IACC-appointed expert panel. The research agenda identified roadblocks hindering progress in understanding autism's causes and developing treatment, and provided goals and strategies for the next 10 years to overcome these challenges. These research efforts will be carried out through the centers of excellence within the STAART network.

PRACTICAL CLINICAL TRIALS

To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin at "the bench" with basic research where scientists study the mechanisms and pathogenesis of a disease at a molecular or cellular level—then progress to the clinical level, or the patient's "bedside." Equally important is the translation from bedside to practice. Moving new drugs and therapies more quickly and smoothly out of the research environment and into the hands of clinicians is a key feature of the NIH Roadmap. To achieve this, NIH will promote the creation of better integrated networks of academic centers that work jointly on clinical trials and which include community-based physicians who care for large groups of patients. Implementing this vision will require new ways of organizing the methods in which clinical research information is recorded, defin-

ing new standards for clinical research protocols, and creating new models of cooperation between NIH and patient advocacy alliances.

For its part, NIMH is finishing up four large-scale, longitudinal research studies to compare therapeutic approaches for serious mental illnesses, including schizophrenia, Alzheimer's disease, major depression, and bipolar disorder. These are different than most clinical trials, which are usually of short duration and limited to assessment of clinical symptoms. The NIMH studies are testing the various treatment options currently available for these disorders in diverse community populations, recruiting people from a variety of "real world" practice settings, and expanding outcome measures to include functional status and economic costs. The clinical populations currently enrolled in these NIMH treatment trials are among the largest and best characterized populations with bipolar disorder, schizophrenia, and depression ever studied through clinical trials in mental health. These trials will answer urgent questions about the treatment of adolescents with depression, the use of atypical anti-psychotics in people with schizophrenia and Alzheimer's, and the optimal long-term medication for bipolar patients. When the studies are over within the next two years, we hope to be able to continue utilizing this valuable clinical infrastructure—made up of staff, investigators, federal and state agencies, industry, patients, and patient advocacy groups—to answer other critical public health questions in diverse populations.

PRIORITY-SETTING

Over the past five years, we have witnessed unparalleled advances in the basic sciences relevant to mental health. Genomics, imaging, and many areas of neurobiology are beginning to reveal a new understanding of normal and abnormal behavior. Against this backdrop of scientific progress, we continue to face extraordinary challenges for our patients with mental disorders. Science now yields opportunities that promise to deliver for each of these challenges. To realize this promise, we must define areas of high priority. To assist us, workgroups of our National Advisory Mental Health Council are reviewing the NIMH portfolio initially in two key research areas: clinical trials and basic science. Both workgroups plan to deliver reports by May 2004 and both will define priority areas using the criteria of relevance, traction, and innovation. Both workgroups have done an impressive job in reviewing the hundreds of relevant grants in the portfolio. We look forward to their recommendations, as well as to those of our Outreach Partners in every state, the mental health advocacy community, and the public. We rely on these groups to help us meet our ultimate goal of relieving the profound misery suffered daily by patients and families affected by mental disorders.

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 2005, a sum of $359,645,000, which reflects an increase of $32,556,000 over the comparable fiscal year 2004 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 the OD in greater detail.

NIH ROADMAP

As part of the NIH Roadmap for Medical Research, the NIH has launched initiatives in fiscal year 2004 critical to addressing the roadblocks to the acceleration of science conduct and transfer to the public. These initiatives promise to yield far-reaching dividends in medical knowledge and improved health for the public. Under the theme of New Pathways to Discovery, initiatives are aimed at quantifying and cataloging complex biological systems and in developing a better "tool box" for today's researchers, for research teams of the future, and for re-engineering the clinical research enterprise. Examples of initiatives include the creation of an accessible public library database for chemically diverse small molecules, centers that will create new tools to describe the dynamics of protein interactions, development of novel technologies to study cellular metabolites, creation of national software engineering system that can facilitate the ability of scientists to tap into supercomputing networks and share and analyze complex data, and the early conceptual development of nanomedicine. The NIH Roadmap initiatives also have taken steps to prepare Research Teams of the Future, the second theme, by encouraging scientists and research institutions, including the NIH, to test alternative models for conducting research that take advantage of the scientific advances and complexities. A major focus has been placed on planning and research workforce training for the conduct of interdisciplinary research, that research that spawns new disciplines of science. In addition, a new award—the NIH Director's Pioneer Award—will support a select group of investigators who have the potential for ground-breading discoveries. Ultimately findings from the laboratory must reach the public, and the initiatives under the third them—Re-engineering the Clinical Research Enterprise—are geared to address the roadblocks to the conduct of clinical research and its translation to patients. These initiatives include the exploration of the ability to create and enhance interoperability among clinical trial networks, the testing the feasibility of establishing a National Clinical Research Associations program where community-based clinicians are trained to participate in studies and play a role in augmenting the transfer of research to their patients, and the assessment of patient-reported chronic disease outcomes. Critical work continues in the area of research policy analysis and coordination with an emphasis on harmonization and standardization of policies and requirements pertaining to clinical research. In addition, extension and expansions of clinical research training programs extramurally and intramurally have been initiated.

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 2005 budget request for OAR is $61,435,000.

THE OFFICE OF RESEARCH ON WOMEN'S HEALTH

The Office of Research on Women's Health (ORWH), the focal point for women's health research for the Office of the Director, strengthens, enhances and supports research related to diseases, disorders, and conditions that affect women, and sex/gender studies on differences/similarities between men and women; ensures that women are appropriately represented in biomedical and biobehavioral research stud-

ies supported by the NIH; and, develops opportunities for the advancement of women in biomedical careers and investigators in women's health research. The report, *An Agenda for Research on Women's Health for the 21st Century*, provides a framework for the ORWH to collaborate with the scientific and advocacy communities to address gaps in knowledge about women's health and sex and gender factors in health and disease. The fiscal year 2005 budget request of $41,577,000 includes an increase of $626,000 over the fiscal year 2004 appropriation.

Research priorities for women's health emphasize the importance of interdisciplinary research with collaboration and integration of knowledge from multiple areas of scientific expertise; lifespan issues and the continuum from intrauterine life into elderly years; health disparities/differences and diversity among different populations or subpopulations of women; and, sex/gender differences in health and disease and therapeutic interventions at genetic, molecular, cellular, and functional levels. Areas of research interest for 2005 include: pathogenesis of diseases including prevalence/validation of sex differences in diagnosis/treatment of disorders/diseases; clinical trial methodology; mental health studies; new agents for management of menopausal symptoms; treatments/interventions for diseases that show enhanced clinical features in women; and other specific areas such as CFS, and benign gynecologic disorders including uterine fibroids. Special emphasis areas for women's health research include genetics/pharmacogenomics, and the genetic, molecular and cellular bases for action of pharmacologic agents known to have differential effects in females; and, prevention and treatment, from basic biological factors to effects of risk behaviors or interventions. There is expansion of new research in the ORWH specialized centers of interdisciplinary research in women's health and sex and gender factors, and the unique ORWH interdisciplinary career development program in women's health research that fosters the mentored development of junior faculty and assists them in bridging advanced training towards a goal of 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 ORWH continues to partner with Institutes and Centers to ensure compliance with NIH policies for the inclusion of women and minorities in clinical research, and that analyses by sex/gender are addressed by investigators funded by the NIH.

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 2005 OD budget includes $26,321,000 for OBSSR, an increase of $415,000 over the fiscal year 2004 appropriation.

Many exciting scientific developments are occurring at the intersection of behavioral and social science research and biomedical research. It has become apparent that increasingly, scientific advances are being made at the interfaces of traditional disciplines, and that approaches to science are becoming more integrative. OBSSR has begun development of a program to provide interdisciplinary training to postdoctoral fellows in NIH intramural laboratories. This program would provide a mechanism hereby an individual with a PhD in a behavioral or social science discipline might acquire interdisciplinary training that included biomedical research. Alternatively, someone trained in a more traditional biomedical field would receive postdoctoral training that included a behavioral or social science component. In addition to the benefits to be realized by the individual trainees, this program would also show NIH leading, by example, our Roadmap efforts to build interdisciplinary Research Teams of the Future.

OBSSR is also developing an initiative to advance discovery of scientific knowledge about eHealth technologies for health behavior change and chronic disease management. Consumers, patients, and providers are increasingly using eHealth applications, particularly the Internet, to seek health information for themselves or family and friends, communicate with others who have a similar disease or illness, and to communicate with their health care providers. These technologies offer people the ability to obtain health information at relatively low cost, including those with limited or no access to health care professionals or services, and historically

underserved populations. While the use of eHealth interventions is becoming widespread, these techniques have yet to receive much rigorous evaluation. This initiative's goal is to bring together components of NIH, the Robert Wood Johnson Foundation and other public agencies and private foundations in a "meeting of the minds" about the state of eHealth evaluation research for health behavior change and chronic disease management, future directions in the field, and the role of NIH and others in developing a research agenda for this area.

Behavioral and social factors contribute significantly to racial and ethnic health disparities. Consequently, OBSSR is committed to developing better knowledge of specific pathways to health disparities and to finding solutions. In February 2003, OBSSR published in the *American Journal of Public Health* a set of papers presenting scientific evidence of the effects of racial/ethnic bias on health and identifying areas for future research to further explicate the relationship. The papers were the product of an OBSSR meeting of approximately 100 leading scientists held in April 2002. Currently, OBSSR is convening discussions among ICs regarding the role of social and behavioral science in their health disparities research activities and avenues for coordinated initiatives.

An effective way to ensure that results of behavioral and social science improve our society's health involves incorporating these in clinical practice. In order to start this process at an early stage in the training of the next generation of physicians, OBSSR funded the IOM to determine how to improve medical education. The results of this study [April 2004] will inform a training initiative that OBSSR with several ICs will launch this year.

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 2005, the Office of Dietary Supplements (ODS) within ODP requests a budget of $26,218,000, an increase of $414,000 over the fiscal year 2004 appropriation. In fiscal year 2004, ODS published its 5-year Strategic Plan for 2004–2009, a major component of which is to significantly expand efforts to address the role of dietary supplements in reducing the risk for chronic diseases. 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.

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 2004 based upon this review, which will serve as the basis for planning further NIH research on omega-3 fatty acids. Congressional language in recent 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 U.S. 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. ODS collaborates with USDA to develop an analytically-based database of dietary supplement ingredients. ODS collaborates with other federal agencies to develop an approach to assessment of the health effects of bioactive factors in foods and dietary supplements. In its continuing efforts to inform the public about the benefits and risks of dietary supplements, ODS collaborates with USDA on the International Bibliographic Information on Dietary Supplements (IBIDS) database, which now includes 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 1999–2002. 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.

Another component of ODP, the Office of Rare Diseases (ORD) was formally established through the Rare Diseases Act of 2002, Public Law 107–280. The purpose of this Act is to increase the national investment in the development of diagnostics and treatments for approximately 25 million patients with more than 6,000 rare diseases. A rare disease is defined as one where fewer than 200,000 persons are affected in the United States. The fiscal year 2005 budget request for ORD is $15,787,600, an increase of $253,000 above the fiscal year 2004 appropriation.

Through its *Extramural Research Program*, the ORD supports a Rare Diseases Clinical Research Network with NIH Institutes and Centers (ICs). The major goals for the network include the systematic collection of clinical information to develop biomarkers and new approaches to diagnosis, treatment, and prevention of rare diseases, and to promote training of new clinical research investigators in rare diseases. ORD funded seven Rare Diseases Clinical Research Consortia and one Data and Technology Resources Coordinating Center. The consortia focus on urea cycle disorders, inborn errors of metabolism, rare neurological channelopathies, idiopathic bone marrow failure states and cytopenias, vasculitides, and defects in steroidogenesis. The patient support organizations are closely integrated into the consortia and the network.

The ORD *Intramural Research Program* promotes training in the areas of clinical and basic research into rare diseases and in biochemical genetics, fosters protocol-based initiatives into rare diseases not currently investigated in the intramural program, assists in the investigation of select, unique disorders of unknown etiology, provides overall research support for diagnostics and therapeutics of rare disorders, and supports five Bench-to-Bedside grants.

In its *Scientific Conferences Program*, in fiscal year 2004, the ORD will cosponsor more than 70 scientific conferences on rare diseases. The 460 conferences sponsored to date since 1995 have been shown to be excellent venues to establish a research agenda for specific rare diseases, take advantage of scientific opportunities, or eliminate barriers to dvancing research.

To provide more comprehensive 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/or rare disorders. In its third year of operation, the information center broadened its language base to include Spanish in addition to English.

In fiscal year 2004, ORD plans to establish a *Trans-NIH Rare Diseases Working Group* to encourage collaborative research activities, provide opportunities for input as new rare diseases research programs unfold, and gather information about the rare disease research programs supported by the ICs and Offices for mandated annual and biennial reports.

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 cre-

ated 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 2005 Budget request for OSE is $3,899,000.

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 2005 Budget request for OLRS is $7,250,000.

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

PREPARED STATEMENT OF DR. PATRICIA A. GRADY

Mr. Chairman and Members of the Committee: The fiscal year 2005 budget includes $139.198 million, an increase of $4.497 million over the comparable fiscal year 2004 appropriation level.

I am pleased to be here today to discuss the activities of the National Institute of Nursing Research (NINR). NINR supports research that converges well with NIH's top priorities and activities. Our research emphases are also reflected in the NIH Roadmap, the strategy to accelerate scientific discoveries and take new approaches to make them more rapidly available to patients. NINR's scientific community is excited about the opportunities within the current and future NIH Roadmap initiatives. NINR is already supporting important interdisciplinary research training and interdisciplinary research, including community-based research. NINR's scientific community has been alerted to the procedural changes that need to take place in order to capitalize on the NIH Roadmap initiatives; their enthusiasm predicts a high level of support for the Roadmap.

From its inception, NINR has emphasized interdisciplinary research teamwork and clinical and translational research, which are prominently featured in the Roadmap agenda. Our studies address national health problems head on. We have moved from an acute to a chronic disease focus, with emphasis on older people, who are living longer with illness and want the highest quality of life possible. We promote ethnically and culturally sensitive research and are aggressively pursuing research on health disparities, devoting about 20 percent of our budget to this area of science.

CONTROL OF HIGH BLOOD PRESSURE IN YOUNG INNER-CITY AFRICAN-AMERICAN MEN

A good example of a program of research that improves health care disparities in a vulnerable African-American population is located a short distance from here—East Baltimore. The number of people with hypertension nationally is 40 percent higher for African-Americans than for Caucasians, and there is more severe disease impact among African-Americans that can include heart enlargement and kidney dysfunction. The Johns Hopkins School of Nursing conducted this unique hypertension study, targeting a high-risk population of hypertensive young African-American men between 21 and 54 years of age who are generally considered underserved by the healthcare system. At the study's start, only 17 percent had control of their blood pressure, but after three years, 44 percent of the men receiving the intensive form of a carefully designed community-based intervention attained control of their blood pressure. In some cases, the study represented the first time the study participants experienced formal healthcare. Of special significance is that 90 percent of the young men were retained in the study for the entire three-year period. A key to this success was the culturally appropriate, multidisciplinary research team approach that involved nurse practitioners, community health workers, and physicians.

Among the lessons learned from this research is the need to modify healthcare for vulnerable populations like this one in Baltimore—health care that involves home visits that offer educational and behavioral counseling to supplement visits to the clinics, and addresses factors beyond the disease itself, such as reducing substance abuse and obesity.

HEALTH OF MINORITY, INNER CITY NEWBORNS IMPROVED BY NURSE HOME VISITS

Another example of a health disparity is infant mortality, with rates for African-Americans twice those of Caucasians. Researchers tested a carefully designed intervention tailored to the risks of the populations studied to help close this health disparity gap. Findings after one year of the project indicate that the health outcomes of both mother and infant were improved, and costly health care was avoided. The intervention involved focusing on low-income, pregnant African-American and Mexican-American mothers from the inner city, who received a program of planned prenatal care and post-natal monitoring with teaching and counseling at each encounter. Home visits made by a team of trained community residents and led by a nurse were an important feature, and the mothers received monthly phone calls for a year after their babies were delivered. The effects of the program varied by race and ethnicity. For African-Americans, findings indicated that mothers had more realistic expectations of their parenting role and were able to document the immunization of their infants. Their infants' mental development scores were higher than the control group. Mexican-American mothers showed improved skills in dealing with everyday life and in playing with their infants. This research and previous studies indicate that home visits by a nurse-health advocate team are among the most successful interventions in improving maternal and infant health—even for-inner city, low-income minority families. The key is to implement culturally sensitive interventions that are intensive and adequately staffed and funded.

WOMEN'S EARLY WARNING SIGNS OF HEART ATTACK

Although heart disease is the number one cause of death in both genders, far less is known by physicians and by women themselves about how women experience the disease. Research focusing on women's symptoms prior to heart attack found that women have different early warnings of heart attach than men have. Of note is that most clinicians consider chest pain as the most significant symptom for both sexes. Yet in this study the most prevalent symptom was reported to be unusual fatigue (70 percent), followed by sleep disturbance (48 percent), and shortness of breath (42 percent). Fewer than a third of the women reported chest pain or discomfort. Even during the heart attack, 43 percent did not experience chest pain. Clearly, women's symptoms appear to be different from men's. This underscores the importance of women and clinicians, both, recognizing early warning signs of impending heart attack in women, so that they can prevent it or ease its effects.

CHOLERA REDUCED BY LOW TECH WATER FILTRATION

A growing global problem faced by developing nations is the availability of healthy drinking water, a most basic need for life and health. Cholera is carried by untreated surface water and kills thousands of people around the world by causing severe vomiting and diarrhea. The World Health Organization reports that the number of countries with cholera is increasing. In our own hemisphere, cholera incidence is now increasing in 16 Latin American nations. Researchers in Bangladesh have found a simple preventive technique that works and may be transferable to other countries. Inexpensive and widely available cotton sari cloth, when folded four to eight times, creates a filter small enough to remove most plankton, where cholera bacteria often live. In 65 villages with 133,000 inhabitants, the number of cholera cases was almost cut in half when people filtered their water with the sari cloth. Cultural barriers were not an issue, and about 90 percent of the rural study participants followed the filtering procedure. When cholera did occur, those villagers had drunk unfiltered water at villages not participating in the study. The sari filtering technique could work just as well using other types of inexpensive cloth filters if replicated in countries where cholera is widespread.

THE NINR ROLE IN THE NIH ROADMAP

Last year, NINR developed what we call Research Themes for the Future, which represent NINR priorities over the next five plus years. These themes blend well with the NIH Roadmap overall, especially in two areas—Interdisciplinary Research Teams of the Future, and Re-engineering the Clinical Research Enterprise. In the first area, NINR has considerable experience carrying out interdisciplinary team re-

search projects. In fiscal year 2003, more than half of NINR investigator publications appeared in non-nursing journals. This underscores the promise of future successful interdisciplinary research and practice collaborations. It also indicates that many other disciplines value nursing research findings. In the area of improving the clinical research enterprise, most of NINR's research is clinical in nature and can bring research questions to the laboratory from the clinical researcher's perspective. Investigators also translate research findings into the clinical practice of healthcare providers and develop partnerships with communities to speed new scientific knowledge into mainstream health regimens. Late last year, NINR supported a national conference to promote research-intensive environments in clinical settings, including academic medical centers and those that are nontraditional as far as research is concerned, such as nursing homes and community-level health enterprises. The goal was to create partnerships between academic researchers and potential investigators in these settings to develop resources and ease barriers to innovative research.

To make the Roadmap a reality for nurse researchers, since the Roadmap will not be business as usual, but business as usual plus, NINR recently convened an implementation meeting with interdisciplinary experts from across the country. The meeting addressed ways to intersect NINR's themes and priorities with those of the Roadmap, as well as suggestions for new Roadmap directions that reflect the expertise of nursing research. Since NINR has always stressed interdisciplinary research, we look forward to increased participation in the Roadmap.

INITIATIVES

Looking ahead to our fiscal year 2005 initiatives, reduction of obesity, a major public health issue, is certainly on the NINR agenda. Pediatric and adolescent obesity is particularly disturbing in and of itself, because it forewarns of future poor health. We plan to target minority populations at risk for obesity and children who are underserved—for example, those in rural areas. Research will address biological, behavioral and social science factors leading to or perpetuating obesity.

Our genetics initiative is novel for NINR, since it involves incorporating behavioral, biological and molecular science into nursing research. Our focus will be on the interactions between genes, environment and behavior, including health promotion behavior. We will also assess the results of genetic education and counseling, and the effects of genetic testing on health, including lifestyle changes and the reduction of risks for disease.

Increased attention is required to build the knowledge base for effective end of life care. NINR is the lead Institute at NIH for end-of-life research. The research agenda we have identified for better healthcare management at this final stage of people's lives includes improved methodology, instruments, communication, and interventions that helped making choices. Previously published NINR-funded research findings on symptom management are already being integrated into standards of care. Further study is taking place to develop new behavioral approaches to improve the lives of patients and their caregivers and to devise new techniques to improve management of pain.

Self-management has become the most basic way people can improve their lives when they are living with long-lasting, incurable chronic illness. Successful self-management interventions tested in mainstream populations, such as how to improve coping skills and how to maintain and improve cognitive functioning, will be tested in populations with special needs: the unemployed, homeless, very old, impoverished, disabled, or geographically isolated.

Another initiative involves symptom management. Traditionally, clinical practice treats symptoms one symptom at a time. Yet symptoms rarely occur alone they occur in clusters. NINR plans to support research that will identify and describe groups of symptoms in HIV/AIDS and cancer patients by determining these clusters' effects on the patient, and developing interventions to manage the multiple symptoms. In addition to assisting how one symptom impacts the others in a cluster, we will consider the effects of age, treatment, gender, and type and stage of disease.

NINR will expand on past and current research initiatives that focus on minority and underserved women's health, such as health disparities and reduction of low birth weight among minority women. The new initiative will focus on other aspects of women's health outside of reproduction, which in the past was frequently the central focus of women's health research by investigators of many disciplines.

INCREASING THE NUMBER OF NURSE INVESTIGATORS

The well documented and current shortage of nurses was preceded by a significant shortage of nurse researchers. The shortage of nurse researchers also means fewer nursing faculty to train future nurses and to conduct research that provides

the scientific base for healthcare practice. In confronting this issue, NINR continues to collaborate with universities nationwide to rapidly develop baccalaureate-to-doctoral fast-track programs. This is in response to one of the recommendations of the National Research Council four years ago, which urged preparation of more nurse researchers more quickly. NINR revised the predoctoral training mechanism to enable nurses to enroll in the many fast-track doctoral programs in nursing which accept baccalaureate-to-doctoral students. NINR has been responsive to the National Research Council's recommendation, and the nursing community has also responded by rapidly developing these baccalaureate-to-doctoral programs all over the nation.

NINR supports Developmental and Core Centers to stimulate research and research training opportunities. Creating partnerships and leveraging funds is a hallmark of those Centers. We also initiated 17 Nursing Partnership Centers to Reduce Health Disparities, in collaboration with the National Center on Minority Health and Health Disparities. These Centers partner eight research-intensive universities with nine minority-serving institutions. As a result of this program, we expect health disparities research to expand and the number of minority nurse investigators to increase.

NINR will continue to offer career development awards, and we will make a special effort to train minority investigators through mentored research scientist awards and research supplemental awards. NINR's small but growing intramural research program is initiating a graduate partnership program with universities across the country this year and continues to support postdoctoral training opportunities on the NIH campus.

In closing, the upcoming year contains new opportunities to configure scientific research in new ways. NINR and the nursing research community look forward to participation in the NIH Roadmap initiative and in other research that directly impacts the improvement of people's health.

Thank you, Mr. Chairman. I will be pleased to answer any questions the Committee might have.

PREPARED STATEMENT OF DR. BARBARA ALVING

I am pleased to present testimony before this Committee on behalf of the National Heart, Lung, and Blood Institute (NHLBI).

The NHLBI leads a national program directed at alleviating the burdens of diseases of the heart, blood vessels, lungs, and blood. The Institute also is responsible for research on the clinical uses of blood and its products and the management of blood resources. For more than a decade, the National Center on Sleep Disorders Research has been part of the NHLBI and, since fiscal year 1998, the NIH Women's Health Initiative has been administered by the Institute. Our diseases and the burdens associated with them touch the lives of all Americans.

BASIC AND CLINICAL RESEARCH APPROACHES

The ultimate goal of the NHLBI is to improve the public health through discovery of effective methods to prevent and treat disease. Progress toward this goal depends on the existence of a coordinated program that focuses on clinical investigation as the culmination of basic research to unravel the fundamental processes that govern health and disease. The Institute has fostered and sustained a longstanding commitment to laboratory investigations of relevance to its mandate. Moreover, in recent years it has allocated a significant share of the generous budget increases provided to it to aggressive pursuit of promising, cutting-edge opportunities in such disciplines as genomics, proteomics, and nanotechnology. Advances in these areas promise to enable, among other things, more specific approaches to health promotion based on detailed assessment of individual characteristics rather than on general observations about what does or does not foster good health. Our optimism about the probable yield of these new endeavors cannot be overstated.

However, the health-related outcomes of these basic science endeavors depend greatly on the extent to which laboratory discoveries are translated into approaches applicable to "real-life" health problems. And that, in turn, depends on clinical research. Being a disease-oriented agency, the NHLBI has for many years placed strong emphasis on developing and maintaining a robust clinical research portfolio. Particularly with regard to clinical trials, the Institute has worked to design efficient, less costly research approaches to evaluating therapeutic and preventive strategies. As part of this effort, the NHLBI has developed and refined the "clinical research network" concept and successfully applied it to evaluate new therapeutic approaches to conditions such as pediatric cardiovascular disease, asthma, acute respiratory distress syndrome, and Cooley's anemia. The networks provide an infra-

structure that enables rapid and cost-effective testing of new therapies as they come to light.

THE NIH ROADMAP—CLINICAL RESEARCH

It naturally follows that the NHLBI is an enthusiastic participant in the NIH Roadmap initiative titled Re-Engineering the Clinical Research Enterprise: Feasibility of Integrating and Expanding Clinical Research Networks. This new solicitation seeks to identify ways in which clinical research networks can collaborate to conduct clinical trials and other multicenter clinical research studies more efficiently than the current system allows. We at the NHLBI believe that application of lessons learned from this Roadmap initiative will better position the Institute to accelerate the pace of research and to reduce barriers that prevent research advances from becoming incorporated into clinical practice.

POSTMENOPAUSAL HORMONE THERAPY

Major unexpected findings from the NIH Women's Health Initiative (WHI) illustrate the critical importance of the randomized, controlled clinical trial in determining the risks and benefits of preventive strategies. The study, which assessed the role of estrogen therapy, with or without added progestin, in preventing major causes of death and disability among postmenopausal women, was predicated on strongly suggestive evidence from basic research, observational studies, and smaller clinical trials that often measured so-called surrogate end points (e.g., changes in heart disease risk factors or subclinical manifestations), rather than events such as heart attacks or deaths from coronary disease. Indeed, at the outset of the WHI, much doubt existed regarding the feasibility and ethics of conducting the trial, because "everybody" already "knew" that hormone therapy helped women remain youthful and "feminine forever," by not only relieving troublesome menopausal symptoms but also improving general health. Much to the surprise of researchers, practicing physicians, and women themselves, the trial of estrogen plus progestin last year was halted when it found increased risks of heart attack, stroke, invasive breast cancer, and blood clots among women assigned to take hormones. And quite recently, the estrogen-alone part of the study was discontinued because the hormone did not appear to have the hoped-for beneficial effect on heart disease (or, on the other hand, the feared unfavorable effect on breast cancer), but it did increase risk of stroke. These findings have major public health significance: the conclusion is that postmenopausal hormones, once ranking among the most-prescribed preparations in the United States, should generally be used only for short-term alleviation of menopausal symptoms.

LUNG-VOLUME-REDUCTION SURGERY (LVRS)

Another trial of great practical importance was a rigorous assessment of LVRS, a procedure that was first used to treat emphysema during the 1950s. Although some patients seemed to benefit from this radical and invasive procedure, high mortality and morbidity discouraged its widespread use until the early 1990s, when some surgeons began performing LVRS again and insurance reimbursement became one of several issues demanding resolution. The National Emphysema Treatment Trial (NETT) clarified the short-and long-term risks and benefits of LVRS and identified the characteristics of patients who may be most likely to benefit from LVRS, as well as those who are at greater risk of death and complications from the procedure. The NETT reflects a unique relationship in which the NIH funded and administered the study and the Centers for Medicare and Medicaid Services (CMS), which sought evidence regarding the advisability of providing Medicare reimbursement for LVRS, supported participants' care costs. Additionally, the Agency for Healthcare Research and Quality contributed support for analysis of the cost-effectiveness of LVRS. The study results have provided a scientific basis for reassessment of Medicare coverage for LVRS.

TRIALS OF HYPERTENSION CONTROL AND PREVENTION

Last year, we reported results from the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), which found persuasive evidence that traditional diuretics should be the initial treatment of choice for lowering high blood pressure. This is a study that only the NIH would likely have undertaken, as the comparison drugs—a calcium channel blocker and an ACE (angiotensin-converting enzyme) inhibitor—were already established as blood-pressure-lowering agents; it further illustrates the unique role played by the NIH in addressing issues of public health importance. Of additional interest is the observation

that blood pressure control rates among ALLHAT participants increased from 25 percent at the beginning of the ALLHAT to 66 percent after five years of followup. These gains were achieved in a variety of clinical practice settings and in subgroups of people known to experience difficulty with blood-pressure control, such as blacks, the elderly, and diabetic patients. These results offer encouragement that blood pressure control is obtainable, and they challenge us to pursue this goal vigorously.

The ALLHAT findings, in combination with evidence from other research studies, prompted issuance of an updated set of guidelines for hypertension management—the so-called JNC 7, or Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment, of High Blood Pressure. An important feature of the guidelines is a reclassification of blood pressure levels that includes the new category "prehypertension" (120 to 139 mm Hg systolic and/or 80 to 89 mm Hg diastolic blood pressure). Individuals with prehypertension are strongly encouraged to pursue lifestyle changes—losing excess weight, eating a heart-healthy diet, increasing physical activity, quitting smoking—to forestall development of overt hypertension. To date, most behavioral interventions have focused on only one or two lifestyle changes at a time. However, findings from a recent clinical trial indicate that an all-in-one approach to lifestyle changes is feasible and effective in lowering blood pressure. Trial participants who addressed many elements of a healthy lifestyle simultaneously also significantly reduced their weight and became more fit providing even more incentive to undertake such changes.

HYDROXYUREA THERAPY FOR SICKLE CELL DISEASE

A breakthrough for patients occurred in 1995 when the NHLBI announced the results of a major trial of the first treatment for adults with sickle cell disease. The study found that use of the drug hydroxyurea slashed rates of painful crises and acute chest syndrome, and sharply reduced the need for blood transfusions and hospitalizations. A followup study of the trial participants recently reported that hydroxyurea not only protects patients from episodes of severe illness associated with their disease, but also prolongs their lives. Even the sickest patients—those who suffered three or more painful crises a year—benefitted. These results have important implications both for improving patient care and for decreasing health care costs associated with sickle cell disease.

IMPROVING SURVIVAL FOR VICTIMS OF CARDIAC ARREST

Cardiac arrest—in which the heart stops beating effectively, blood does not circulate, no pulse can be felt, and the victim collapses into unconsciousness—is a frequent occurrence in this country. Despite several decades of efforts to train members of the public to perform CPR (cardiopulmonary resuscitation), few victims of out-of-hospital cardiac arrest survive the experience. The NHLBI Public Access Defibrillation trial trained volunteer rescuers to use an automated external defibrillator, a device that shocks the heart back into normal rhythm. It found that use of CPR plus the defibrillator, compared with use of CPR alone, markedly increased survival of people who suffered cardiac arrest in various community settings, and caused no major injuries or serious safety problems. An important next step, currently under way with NHLBI support, is to determine the safety and effectiveness of providing defibrillators to families of heart attack patients for use when a cardiac arrest occurs at home. In addition, the Institute is establishing a research consortium of investigators, hospitals, emergency medical services, and local communities to investigate promising experimental strategies to resuscitate patients who experience out-of-hospital cardiac arrest.

COMBATING THE OBESITY EPIDEMIC

Obesity is a problem of great concern to the NHLBI, as it strongly influences the risk for developing diseases and conditions such as coronary heart disease, hypertension, and diabetes. Thus, the Institute is strongly involved in the overall NIH effort to reverse the U.S obesity epidemic, and I have been especially pleased to serve as cochair of the NIH Obesity Research Task Force.

The NHLBI recently launched a major study that addresses one of the most challenging aspects of weight control—keeping lost pounds off. The Weight Loss Maintenance Trial will initially assist overweight or obese adults participants in making lifestyle changes to reduce their weight and, subsequently, it will test various strategies to help the participants maintain their weight loss over the next several years. The trial focuses on persons who are being treated for high blood pressure or high blood cholesterol and, consequently, have particularly strong reasons to achieve and maintain a healthy weight.

Another new initiative will assess the effectiveness of worksite interventions for preventing or controlling overweight and obesity in adults. Strategies to be considered include implementing environmental and policy changes to increase employees' physical activity (e.g., flextime or fitness-center discounts), offering healthful food choices in cafeterias and vending machines, providing information about nutrient and calorie content of foods at the point of purchase, and enhancing social support from fellow workers to encourage improved diet and physical activity.

A third NHLBI initiative will explore the potential use of bioengineering approaches to address problems of obesity. For example, new methods for imaging body fat content may enable more specific identification of who needs to lose weight and their success in doing so. Bioengineering techniques may also offer a solution to the difficult technical challenge of obtaining precise measurements of energy intake and expenditure. One can envision development of a wristwatch-like gadget from which the wearer could easily determine whether an energy intake goal has been exceeded or an energy expenditure has been met. New approaches might provide accurate, convenient, easily understood, and inexpensive devices that would foster research, improve clinical management of adults and children, and help the public eat less and exercise more.

CONCLUSION

These examples illustrate the extraordinary potential of clinical research, and particularly clinical trials, to address issues of major importance to the public health. The NHLBI will continue its commitment to stimulate and support clinical research, and to ensure that the knowledge thereby gained is rapidly, efficiently, and fully applied to disease treatment and prevention.

BUDGET STATEMENT

The fiscal year 2005 budget includes $2,963.9 million, an increase of $172.1 million over the fiscal year 2004 enacted level of $2,791.8 million.

I would be pleased to answer any questions that the Committee may 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 Communication Disorders (NIDCD). The fiscal year 2005 budget includes $393,507,000 which reflects an increase of $11,561,000 and a 3 percent increase over the fiscal year 2004 final conference level. 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. NIDCD's mission includes the support of research to create assistive devices which substitute for lost and impaired sensory and communication function. Equally important to the NIDCD mission has been the discovery of genetic mutations that affect communication disorders. This work would not have been possible without the completion of the Human Genome project, supported in part by the National Institutes of Health. Enabled by this landmark accomplishment, scientists supported by the NIDCD have been studying the genes responsible for non-syndromic (not associated with any other problem) hereditary hearing impairment. Within the last 8 years, 54 genes have been identified, largely due to the contributions of NIDCD. Scientists are now focusing their efforts on identifying more genes, learning what role the genes have in deafness, and determining which genes affect certain populations of individuals. For example, recent studies have demonstrated that particular ethnic groups carry specific genetic mutations. Studying the genes that cause non-syndromic hereditary deafness will also permit early and more accurate genetic testing and foster the development of innovative intervention and prevention strategies, and more effective treatment methods for individuals with deafness and other communication disorders. My testimony today will primarily focus on the many genetic discoveries that have allowed NIDCD-supported scientists to learn more about the causes of communication disorders, a first step in prevention and treatment.

NEW WAY TO IDENTIFY USHER SYNDROME IN CHILDREN

Usher syndrome Type 1 is an inherited disorder. Children born with this disorder are deaf, suffer balance problems, and gradually lose their vision. Although Usher syndrome affects individuals of other racial and ethnic backgrounds, scientists have recently identified a clear pattern of its inheritance in Ashkenazi Jews, who are de-

scendants of Jews from Germany, Austria and Eastern Europe. In 2003, a NIDCD-supported scientist identified a mutation within the gene known to be responsible for Usher syndrome. The particular mutation seems to be responsible for most of the Usher syndrome seen in Ashkenazi Jews. Because scientists now know which mutation is responsible for this type of Usher syndrome, they can develop genetic tests to detect the mutation in Ashkenazi Jewish children who are born deaf. By identifying children destined to lose their sight, parents and doctors can help them learn to communicate and prepare them for blindness. Some of these children will be appropriate candidates to receive a cochlear implant. Cochlear implants are small electronic devices that enable individuals who are deaf or have severe hearing loss to detect sound. This research will now enable doctors to provide important quality of life improvements for children with Usher syndrome.

GENE REPLACEMENT THERAPY CAN GENERATE NEW HAIR CELLS

The sensory hair cells of the inner ear play an important role in detecting sound. People who lose hair cells due to excess noise, infections, or accidents often lose some or all of their ability to hear. Scientists have determined that many forms of inherited deafness are also due to problems with hair cells. The hair cells of the inner ear act like miniature amplifiers. Sound waves that enter the inner ear are converted into a series of chemical and electrical signals within the cells. These signals are ultimately transmitted to the brain via the auditory nerve and interpreted as sound. In the past, only birds or reptiles were thought to be capable of generating new hair cells. Now, NIDCD-supported scientists have discovered a way to use gene therapy to generate new hair cells in the ears of adult mammals. Scientists used a virus to transfer a gene called Math1 into the ears of guinea pigs. Math1 is expressed in developing hair cells, and its expression is thought to cause the cells to become hair cells, rather than becoming another cell type within the ear. The virus infects cells of the ear and causes them to produce the Math1 protein. Early experiments suggest that when the virus infects cells that do not normally express Math1, some of these cells become hair cells. In addition, the new hair cells also attract fibers of the auditory nerve, suggesting that the new cells may also be able to establish a link to the part of the brain that interprets sound—the auditory cortex. If this work can be duplicated in human beings, it may be the first step towards enabling scientists to use gene therapy to restore hearing to those who have lost it, or to enable deaf individuals to hear.

NEW SHORT ELECTRODE WILL ALLOW GREATER BENEFIT FROM COCHLEAR IMPLANTS

Cochlear implants are commercially available miniature hearing prostheses capable of assisting those who are profoundly deaf or severely hearing impaired. Approximately 60,000 individuals all over the world have received cochlear implants. The implant bypasses damaged or missing hair cells to send electrical signals through an array of electrodes within the cochlea (inner ear). Current cochlear implants send sound information that covers the entire frequency range. In order to send both high and low frequency information, the electrodes of the cochlear implant are inserted as far into the cochlea as possible. Unfortunately, inserting the electrodes into the cochlea compromises any residual (remaining) hearing the individual may have had prior to implantation. Consequently, scientists developed a new shorter electrode to help an additional population of individuals with hearing loss. These individuals have a considerable amount of residual hearing and their primary hearing loss is in sounds in the high frequency range. They are also experienced, yet unsuccessful, adult hearing aid users with severe-to-profound hearing impairment who would not have been conventional cochlear implant candidates. The short electrode is inserted into the base (or bottom) of the cochlea to restore hearing at high frequencies, while preserving low frequency hearing, or residual hearing, in the apex (or top) of the implanted ear.

The preliminary data demonstrates residual hearing can be preserved with this short electrode, and provides evidence that this is most beneficial for understanding speech in a noisy background. Furthermore, the innovative short electrode may be an ideal treatment for those with presbycusis, which is the loss of hearing that gradually occurs in most individuals as they grow older. This new electrode design allows many more people with some degree of hearing loss to benefit from cochlear implant technology.

IDENTIFYING GENES IMPORTANT FOR THE SENSE OF TASTE

The worldwide obesity epidemic is causing health professionals to focus their attention on how people choose which foods to eat. Because taste plays an important role in food choice, scientists are interested in figuring out how taste buds tell the

brain that they have tasted something, and which taste genes are responsible for sensing different food flavors. Vegetables such as broccoli, cauliflower, cabbage, and brussels sprouts contain compounds related to phenylthiocarbamide (PTC). For more than 50 years, scientists thought that the ability to taste PTC and similar compounds was determined by a single gene. If an individual inherited the PTC-tasting version of the gene, then they detected its bitter taste. If the tasting version of the gene was not inherited, the compound had no taste to that individual. Now NIDCD scientists, in collaboration with scientists in California and Utah, have identified a gene that regulates a person's sensitivity to the bitter taste of PTC. This explains why people seem to demonstrate a range of sensitivity to PTC's taste and may even influence whether or not an individual likes to eat broccoli and other vegetables containing PTC-like compounds. Because they determine an individual's sensitivity to a particular taste, inherited genes probably influence food choices. In the future, doctors may now be able to use this knowledge as part of a strategy to prevent and treat obesity and to overcome poor nutrition due to poor food choices. Increased knowledge about how taste cells tell the brain that they have detected a particular flavor may also help doctors restore the sense of taste to those who have lost it due to injury, disease or aging.

VOCAL FOLD PARALYSIS

Vocal fold paralysis is a genetic disorder that can be inherited. The vocal folds are two bands of smooth muscle tissue that lie opposite each other and are located in the larynx or voice box. When at rest, the vocal folds are open to allow an individual to breathe. Voice is produced by vibration of the vocal folds. To produce voice, air from the lungs passes through the folds, causing vibration and thus making sound. The sound from this vibration then travels through the throat, nose, and mouth (resonating cavities). The size and shape of these cavities, along with the size and shape of the vocal folds, help to determine voice quality. Paralysis of the vocal folds impacts voice quality and inhibits an individual's ability to communicate. This disorder can also cause life-threatening breathing difficulties in affected newborn infants.

Intramural scientists at the NIDCD and the National Institute of Neurological Disorders and Stroke are studying a family in which this disorder occurs and have found that vocal fold paralysis is due to degeneration of the nerves involved in movement. Weakness in the muscles of the arms and legs can also accompany this disorder. In the study, genetic analyses were used to locate the site of the causative gene to a section on chromosome 2. Further studies revealed that mutations in the dynactin gene, which resides at this location, are responsible for this disorder. Dynactin is a molecule that helps transport materials within nerve cells, and this research finding suggests that dynactin transport is essential for health and maintenance of at least some motor nerve cells.

This finding allows for a genetic tool for diagnosing vocal fold paralysis, which can aid in the clinical and neonatal management of this disorder. In addition, these findings provide better understanding of motor nerve cells and the molecular mechanisms that cause motor nerve degeneration.

NIH ROADMAP

The NIH Roadmap initiative to support interdisciplinary research and research training will advance the NIDCD mission because it encourages collaboration of scientists from seemingly unrelated disciplines. Interdisciplinary collaborations from a variety of scientific disciplines are necessary for developing assistive communications devices such as hearing aids and cochlear implants. The success of the development of the cochlear implant is a good example of successful interdisciplinary research as it involved the effort of physicists, chemists, material scientists, psychologists otolaryngologists, audiologists, speech-language pathologists, electrical engineers, and biomedical engineers We look forward to expanding upon that type of research in the coming years.

Finally Mr. Chairman, I would like to thank you and Members of this Committee for giving me the opportunity today to speak to you about the exciting recent discoveries from the NIDCD. I am pleased to answer any questions that you have.

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

2005, a sum of $325,147,000, which reflects an increase of $16,671,000 over the comparable fiscal year 2004 appropriation.

The National Library of Medicine continues to be the premier source of science-based medical information. Just 10 years ago the Library introduced its Web site one of the very first in the federal government and so began a decade of amazing growth in the amount and variety of medical information it made available. Today the Library's Web service not only provides free access to Medline/PubMed, the largest and most reliable database of scientific medical information in the world, but NLM has created information products designed specifically for patients, families, and the public.

Despite its recent successes, NLM believes that the surface has barely been scratched and that the future holds the promise of many more valuable information products for the professions and the public. The Library's communications experts are at the cutting edge of new technology and, as more and more users have access to ever more powerful networks, the Library will put in place sophisticated yet easy to use information services that allow users free access to the world's burgeoning base of science-based health information. For scientists this means access not only to the growing published journal literature, but also electronically to scientific monographs and textbooks and to a variety of genomic information resources through NLM's National Center for Biotechnology Information (NCBI). For the general public, this means making even more consumer health information—from the National Institutes of Health and other reliable sources—available from the NLM's Web site.

The new NIH Roadmap Initiative has the potential to have a profound and positive impact on how American medical research is conducted. The NLM sees itself has having an important role in the Initiative in three areas. Because the Roadmap recognizes that one of the most powerful and unifying concepts of 21st century biology is that of bioinformatics, the computerized bioinformatics databases and analysis tools of the NCBI will become even more central to the research enterprise. Second is the Roadmap's requirement to "re-engineer the national clinical research enterprise." NLM's leadership role in working with biomedical vocabularies the Unified Medical Language System, the recently announced arrangement with the SNOMED clinical vocabulary, and NLM's expanding the NIH clinical trials database are all key aspects of improving clinical research. Finally, the Roadmap articulates NIH's responsibility to communicate research results to improve the quality of life for all people. The Library has a central role in collecting and communicating these results through Web-based information services and online databases. These are described in what follows.

TOOLS FOR SCIENTISTS AND HEALTH PROFESSIONALS

The NLM's Medline/PubMed is the most-used database of peer-reviewed medical information in the world. It contains more than 12 million references and abstracts to the world's medical literature published since the 1960s; an ancillary "OldMedline" extends the coverage back to the early 1950s. Each year millions of scientists and health professionals connect to Medline/PubMed (no registration or fee is required) and search for information they can use in the research or practice. More than a half billion such searches are done every year. The newest system, introduced in 1997, is constantly being improved. Several years ago NLM introduced links between Medline/PubMed references and publisher websites so users could retrieve the full text of articles. Today, more than 4,000 of the database's 4,600 publications have such links.

Another heavily used database is GenBank, the repository of all publicly available DNA sequences sent to the NLM from laboratories around the world. GenBank, and an increasing array of other valuable data resources, is the responsibility of the National Center for Biotechnology Information. The Center, which was created by the Congress in 1988 with the mandate to manage and disseminate genetic data, coordinates closely with the NIH Human Genome Project. GenBank today contains more than 27 million sequence entries totaling 33 billion base pairs from over 130,000 species. NLM, through the Web operations of the NCBI, 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.

A repository for chemical structure and assay data has been suggested as one aspect of NLM's involvement with the NIH Roadmap Initiative on "small molecules" to enhance research and develop new therapies. The NCBI is working on such a repository—called PubChem—which will integrate into one open database, information from existing chemical structure databases at various NIH institutes as well as data supplied from industry and academic centers. By providing chemical structure validation and structure-structure matching and by linking to descriptions of

the compounds in journal articles, PubChem will play an invaluable role in making this information useful to scientists.

PubMedCentral, a digital archive, is an important component of the infrastructure needed to enhance access to the life sciences literature. Publishers electronically submit peer-reviewed research articles, essays, and editorials. NLM guarantees free access to the material; copyright remains with the publisher or the author. Access to PubMedCentral is free and unrestricted. The full text of more than 100 life science journals, some going back decades, is now available, and more are added as they sign on to the system. Digitally archiving the scientific literature and guaranteeing access for future generations is an important NLM responsibility.

INFORMATION SERVICES FOR THE PUBLIC

The National Library of Medicine has become a favorite destination of seekers of health-related information on the Web—people looking for answers to questions about their health or the health of their loved ones. MedlinePlus, the largest of NLM's Web offerings for the general public, now receives about 4 million unique visitors a month. Increasingly, they also find their way on the NLM Web site to other services created specifically for them—NIHSeniorHealth.gov, ClinicalTrials.gov, Genetics Home Reference, Household Products Database, and Tox Town are all recent examples. These Web sites contain or point to information created by NIH components and other reliable noncommercial sources. They require NLM librarians and information specialists to work closely with a wide variety of outside organizations. MedlinePlus, launched in November 1998, today is one of the most heavily trafficked Web sites containing health information for the public. It has more than 650 "health topics," containing, for example, overview information, pertinent clinical trials, alternative medicine, prevention, management, therapies, the latest research, and the latest news from the print media. There are even links to the scientific literature through Medline/PubMed. In addition to the 650 health topics, there are medical dictionaries, encyclopedias, directories of hospitals and providers, and interactive "tutorials" with images and sound. MedlinePlus en español was introduced in 2002 and has grown to virtual parity with the English version. Both scored the highest marks of any Federal Web site in a recent outside evaluation. A new aspect of MedlinePlus is its plan to "Go Local," that is, to link users with community helping services near them. North Carolina is the first MedlinePlus partner to go local.

The National Library of Medicine is collaborating with the American College of Physicians in a unique "Information Rx" project that seeks to encourage practicing physicians who are members of the College to "prescribe" MedlinePlus to their patients who need further information on a medical subject. After test runs in Georgia, Iowa, Virginia, and Florida, the Information Rx program will go nationwide later in 2004.

MedlinePlus is not the only NLM information service directed at the consumer. Another very popular resource is ClinicalTrials.gov, which integrates previously fragmented information on human studies for different conditions into a single, coherent system, providing the public with an easy-to-use and convenient "one-stop" site for comprehensive information on clinical trials. The site, which is used not only by the public but by their health care providers, currently includes information on approximately 8,800 trials for hundreds of diseases and conditions conducted in about 90 countries. ClinicalTrials.gov receives approximately 16,000 visitors daily and over 3 million page views monthly.

Late in 2003 another service for the public was launched: NIHSeniorHealth.gov. This site contains information in a format that is especially usable by seniors. For example, the site features large print and easy-to-read segments of information repeated in a variety of formats—such as open-captioned videos and short quizzes to increase the likelihood it will be remembered. NIHSeniorHealth.gov has a "talking" function, which allows users the option of reading the text or listening to it as it is read to them. Another new NLM consumer service is the Household Products Database. This is a guide that provides easy-to-understand information on the potential health effects of more than 2,000 ingredients contained in more than 4,000 common household products. The database provides information on many of these substances and their potential health effects, in consumer-friendly language. For more technical information, users can launch a search for a product or ingredient from the product's page into NLM's TOXNET, a cluster of databases on toxicology, hazardous chemicals, and related areas.

Another consumer health information resource introduced in 2003 is the Genetics Home Reference. Genetics is a complex subject, and much of the primary data and literature are difficult to understand without formal training. The Genetics Home

Reference Website augments MedlinePlus with summaries of genetics information and an overview of the fundamentals of genetic science. The user can browse by a specific disease/condition or by gene. It also has a geographic list of genetic counselors and information for care-givers. The database has more than 100 condition summaries and 80 gene summaries and new content is being added continuously.

The Library launched Tox Town late in 2002. Tox Town looks at an ordinary town and points out many environmental hazards that might exist there. Users can click on a town location, like the school, and see a colorful dollhouse-style cutaway view of that building. Toxic chemicals that might be found in the school are listed, along with links to selected Internet resources about school environments. There are similar cutaways for offices, factories, parks, and other locations. NLM has plans to add new scenes, such as an urban community and a farming region.

SERVING SPECIAL COMMUNITIES

With all these unique information resources, it becomes more and more important for the Library to engage in outreach to let citizens know what is available. The 5,100-member National Network of Libraries of Medicine is an important partner in these outreach endeavors. Many of the programs are directed at minority populations. For example, there are programs to assist in remedying the disparity in health opportunities experienced by African Americans, Latinos, Native Americans, senior citizens, and rural populations. A new NLM database introduced in 2003 has health information aimed at Asian Americans; 2004 will see a similar database with information about the health concerns of Native Americans.

Under a program with the Historically Black Colleges and Universities (HBCUs), NLM is helping to train people to use information resources in dealing with environmental and chemical hazards. The latest aspect of this outreach effort is NLM's collaboration with the United Negro College Fund Special Programs Corporation to work with the HBCUs in the area of consumer health to encourage the use of reliable electronic health information (such as that provided by the NLM) by the public.

NLM also has been instrumental in reaching out to other countries around the world to help improve their access to scientific medical information. The oldest such program is that involving formal partnerships with major institutions in 20 countries. The NLM helps them obtain computerized access to the literature; the countries in turn help NLM receive the medical literature from that part of the world. The Library is also a key player in the Multilateral Initiative on Malaria, the multiagency effort to improve malaria research in African nations. NLM's role is to establish and maintain the first malaria research communications network, MIMCOM. There are now 19 research sites in 9 countries participating, with full access to the Internet.

SCIENCE ADVANCES

Many scientists believe that molecular biology is the primary driver of medical advances in the 21st century. The rapidly increasing volume of molecular data and the need to decipher its cryptic and subtle patterns has created demanding requirements for computerized databases and analysis tools, special curatorial expertise, and unique physical facilities. The National Center for Biotechnology Information is a key player in ensuring that the outpouring of data from molecular biology laboratories around the world is turned to life-enhancing purposes. GenBank, as noted above, is growing rapidly with contributions received from scientists around the world. Scientists also avail themselves of sophisticated computational tools, such as the BLAST suite of programs, which lets scientists search enormous quantities of data for sequence similarities that will identify genes and genetic features. Another tool, Entrez, allows users to search DNA sequences and literature information with techniques that are fast and easy to use. The newest tool is the "Reference Sequence Collection," which provides a centralized, integrated, non-redundant set of sequences that is integrated with other information for all major research organisms. Using the Reference Sequence Collection, time once spent on having to identify, gather, and analyze data can now be spent effectively on research.

The Center is now also conducting research using the human genome sequence to begin exploring the history of human populations. NCBI researchers, working with other collaborators, first assembled a set of 500,000 high-confidence variations and then compared the distribution of these variations on the genome to that predicted by several models of population history. They found that the data best fit a model in which the human population shrank dramatically about 40,000 years ago, a time when modern humans first appeared in Europe. The model suggests that the population subsequently grew about 30,000 years ago, consistent with archaeological evidence of a population expansion during that period. The results indicate that

databases of genetic variation constructed alongside the human genome project can provide a unique insight into the history of human populations. This insight may also explain how these populations may respond differently to selective pressures such as infectious diseases.

NLM's Lister Hill National Center for Biomedical Communications sponsors high-technology communications research projects in such areas as high quality imagery, medical language processing, high-speed access to biomedical information, developing intelligent database systems, multimedia visualization, data mining, and machine-assisted indexing. One prominent area of research has been the Visible Human Project. The project consists of two enormous (50 gigabytes) data sets, one male and one female, of anatomical MRI, CT, and photographic cryosection images. These data sets are available through a free license agreement to 1,800 individuals and institutions in 47 countries where they are being used in a wide range of educational, diagnostic, treatment planning, virtual reality, artistic, and industrial applications. An "Insight Toolkit" has been developed and makes available a variety of open source image processing algorithms for computing segmentation and registration of medical data. The Visible Human Web site is one of the most popular of all NLM's Web offerings.

NLM's Extramural Programs for more than 20 years has supported the training of medical informaticians at universities across the nation. In the early years the program focused on training of informaticians for clinical care. Today the training programs have added opportunities for training in bioinformatics, the field of biomedical computing for the large datasets characteristic of modern research. At present, NLM provides 18 grants to biomedical informatics training at 26 universities, supporting 250 trainees. NLM also participates in the NIH Roadmap activities, almost all of which have major emphasis on biomedical computing. For example, training is an important requirement of the National Centers for Biomedical Computing, an initiative for which NLM is one of the key leaders. Training as embedded in Roadmap activities is expected to become a significant complement to NLM's traditional support of informatics training.

THE FUTURE

In its role as the world's largest medical library, the NLM will continue to provide free access to the enormous literature of the health sciences, including even priceless historical treasures dating to the 11th century. As to the 21st century, the Library is making major contributions to the NIH Roadmap and is also applying its unparalleled collections and talents to "BIOSHIELD," the Department of Health and Human Services' effort to combat bioterrorism. The ability to apply medical knowledge to make our citizens healthy and safe is to repay the investment of the nation in medical research. In this, the National Library of Medicine can be of great help.

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 2005, a sum of $441,911,000, which reflects an increase of $13,486,000 over the comparable fiscal year 2004 appropriation.

As the recent NIAAA National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) has shown, most cases of alcoholism are established by age 25, beginning as early as age 18.[1] These new results, which are corroborated by studies not yet published, call for a major refocusing of research on youth as the most important target for preventing alcohol abuse and alcoholism on a public-health scale. We now know that youth and adolescence are the critical window of opportunity. The earlier one drinks in adolescence, the greater the likelihood that he or she will develop alcoholism.

The public-health implications of preventing alcoholism before it becomes established in youth are large, given the magnitude of alcohol misuse and its consequences. The 2002 report of the World Health Organization ranks alcohol third as a preventable risk factor for premature death in developed nations. Only tobacco and cholesterol are greater risk factors.

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[1] NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003, and unpublished data from the Collaborative Studies on the Genetics of Alcoholism.

In the United States, almost 18 million American adults met the clinical diagnostic criteria for alcohol abuse or alcohol dependence in 2002.[2] Annual costs to U.S. society of the consequences of alcohol misuse are about $185 billion.[3]

Heavy alcohol use in the American military is on the rise, with more than 19 percent of male personnel and more than 5 percent of female personnel reporting heavy use.[4] (The Department of Defense defined heavy drinking as five or more drinks on one occasion, at least once a week, in its survey). This pattern of drinking is hazardous to the health and welfare of the individual, the family, and society. In the general population of the United States, alcohol-related illness and injury account for at least 8 percent of all emergency-room visits.[5]

ALCOHOL USE BY YOUTH

Alcohol is the primary psychoactive substance of abuse by American children. As the NIAAA fiscal year 2005 Congressional Budget Justification notes, 78 percent of 12th graders, 67 percent of 10th graders, and 47 percent of 8th graders have used alcohol.

The same source of those statistics, the National Institute on Drug Abuse's *Monitoring the Future* survey, also indicates that youth who report having been drunk at least once include 62 percent of 12th graders, 44 percent of 10th graders, and 21 percent of 8th graders. Roughly half of those percentages say that they drank heavily five or more drinks in a row in the past 2 weeks.

The NESARC data show that most cases of addiction, not only to alcohol, but also to other drugs of abuse, first occur in youth, after which new cases drop off sharply. The same research shows that, by comparison, new cases of depression do not follow this trajectory, instead continuing to rise after adulthood.

REFOCUSING THE RESEARCH

The new finding that youth is the stage of life during which alcoholism is most likely to begin calls for a shift in the emphasis of our research. By focusing even more strongly than we currently do on developing strategies to prevent the onset of alcoholism in this population, we have the potential to dramatically reduce, overall, the occurrence of this common disease.

Likewise, shifting the focus of our medication development program to the early stages of the disease stands to improve the effectiveness of treatment. As with most diseases, early treatment for alcoholism could prevent a host of problems, including the medical sequelae of heavy alcohol use, which are estimated to cost $18.9 billion annually.

Studies show that a combination of factors underlie drinking behaviors. Environmental factors—family and peers, for example—are the dominating influences on whether or not an individual first uses alcohol. Personality and temperament also influence the decision to begin drinking. These factors have a profound effect on youth.

Whether or not drinking continues also is influenced by differences, from individual to individual, in the pharmacological effects (activities of genes, proteins, and metabolic products) that come into play once drinking has begun. When drinking progresses to alcoholism, alcohol's pharmacological effects will have become the dominant influence on drinking behavior.

Identifying the pharmacological effects of alcohol is essential to our ability to design effective prevention and treatment strategies for youth. In childhood and adolescence, the pharmacological effects of alcohol are occurring at a time of rapid structural and physiological change in the brain. One of the major questions before us is how alcohol's pharmacological effects work in ways that specifically promote alcoholism during this vulnerable time of life. Two NIH Roadmap initiatives will be particularly informative in this regard, as follows.

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[2] Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, Pickering RP. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991–1992 and 2001–2002. Drug and Alcohol Dependence, in press, 2004.

[3] Harwood, H.; Fountain, D.; and Livermore, G. (2000). The Economic Costs of Alcohol and Drug Abuse in the United States 1992 (updated for 1998). Report prepared for the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Department of Health and Human Services. NIH Publication No. 98–4327. Rockville, MD: National Institutes of Health.

[4] The 2002 Department of Defense Survey of Health Related Behaviors Among Military Personnel.

[5] McDonald III AJ, Wang N, Camargo Jr CA. U.S. Emergency Department Visits for Alcohol-Related Diseases and Injuries Between 1992 and 2000, Archives of Internal Medicine, 2004;164:531–537.

The Roadmap Metabolomics Technology Development Initiative will enhance our ability to identify metabolic processes that contribute to alcohol dependence (and alcohol-related organ damage). People have differences in the genes that regulate their cellular mechanisms, including the enzymes responsible for alcohol metabolism. These differences result in variations in how people respond to alcohol; for example, the choice to drink and the amount of alcohol consumed.

Proteins, such as the receptors and transporters for neurotransmitters, play roles in virtually every step of alcohol's actions in the brain and other organs. Another Roadmap initiative, the National Technology Centers for Networks and Pathways, will remove barriers to defining how these proteins behave in the complex biological systems in which they interact. Such proteins are potential targets for medications, but efforts to alter the actions of proteins with potential medication compounds have thus far met with limited success in preventing and treating alcohol-use disorders in adults. This Roadmap initiative will provide much-needed tools that will help us track the interactions of specific proteins at specific points in time and cellular space an ability that will enable us to develop more precise targets for medications to treat the early stages of alcoholism.

ACTIONS UNDERWAY

Our current research on drinking by youth includes studies of the neurobiological mechanisms of adolescent alcohol abuse; an initiative on preventing alcohol-related problems among college students; expanded testing of preventive interventions, from rural children to children in urban, diverse neighborhoods; and an initiative that is examining risk factors and testing community-based, longitudinal prevention programs among children in rural and small urban areas, in response to fiscal year 2004 House Appropriations Report language.

Included in NIAAA's fiscal year 2005 Congressional Budget Justification is an expansion of the latter initiative among youth in rural and small urban communities, both of whom have high rates of alcohol use. Both biological and environmental studies, as well as studies of prevention strategies, will be included. The Substance Abuse and Mental Health Services Administration, the National Institute on Drug Abuse, the National Institute of Child Health and Human Development, the National Institute of Mental Health, and other NIH Institutes, as well as the Department of Education and other Federal agencies, will be invited to collaborate in this initiative.

In addition to our research, we conduct outreach programs for youth. The Leadership to Keep Children Alcohol-Free has recruited 33 Governors' spouses to spearhead a national prevention campaign. The Task Force on College Drinking has brought together university presidents and researchers, and is making headway in efforts to reduce drinking by college students and in evaluating those efforts.

THE LARGER PICTURE

Alcohol abuse and alcoholism often result in behavioral outcomes such as property damage, legal problems, disrupted family lives, and derailed academic pursuits and professional careers. But its consequences also include medical sequelae. With prolonged, heavy use, it can act as a toxin, damaging virtually any organ in the body. For example, alcohol is a leading cause of liver cirrhosis and contributes to some kinds of cancer. Approximately 77 percent of the annual $185 billion cost of alcohol misuse is health-related, generated by medical consequences and lost productivity associated with illness or death.

Research leading to effective strategies for preventing and treating alcoholism early in life, when it is most likely to begin, can help avert many other costly problems. While we will increase our research on drinking by youth, we will continue our studies of the many other facets of alcohol use, such as fetal alcohol syndrome, as well as our research on the apparent protective effect of moderate drinking against certain chronic diseases.

CONNECTION TO OBESITY

We will also conduct research on alcohol's role in the national obesity epidemic. In addition to acting as a drug, alcohol is a food—a highly caloric food. It has more calories per gram than do carbohydrates or proteins.

In addition, alcohol acts on some of the same neurotransmitter systems that regulate appetite. Some medications that work to reduce appetite may also reduce alcohol intake. One of the highest priorities that NIH lists in its Government Performance and Results Act goals is human testing of the compound rimonabant for its potential to reduce alcohol use.

Among the many neurotransmitter receptors that alcohol affects is the one receptor to which the active ingredient in marijuana binds. Stimulation of this receptor promotes appetite, and NIAAA animal studies show that blocking the receptor with rimonabant has the potential to reduce drinking in humans. NIAAA is preparing a human trial of rimonabant for treatment of alcoholism. Rimonabant made news in March of this year, when a French company announced the medication's effectiveness in reducing both weight and smoking.

The anticonvulsant topiramate also is being tested for its effectiveness in reducing both obesity and alcohol use, through actions on another neurotransmitter system. The neurotransmitter gamma-aminobutyric acid (GABA), among many others, is known to be an important intermediary of alcohol's actions in the brain.

Obesity and alcohol are linked in yet another way, recent studies show. The livers of obese rats undergo more cell death and sustain more injury from heavy, periodic alcohol use than do those of their slimmer counterparts. In humans, liver damage is one of the most prevalent medical consequences of chronic drinking.[6]

IMPLICATIONS

On a large scale, epidemiology tells scientists where the action is. That is the case with our new findings on the stage of life when alcoholism is most likely to develop; that is, by age 25. We are beginning to take steps to greatly increase our focus on this period—on how variations in genetic, biological, and environmental factors unfold to promote establishment of alcoholism during development. Meanwhile, the NIH Roadmap initiatives on metabolomics and proteomics are developing tools that can significantly accelerate our research.

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 2005. The fiscal year 2005 budget includes $394,080,000, an increase of $11,032,000 over the fiscal year 2004 level of $383,048,000 comparable for transfers proposed in the President's Request.

DELIVERING ON THE PROMISE OF BASIC RESEARCH

Although highly technical in nature, basic research provides the detailed molecular clues that scientists and clinicians can use to develop new strategies that more effectively prevent or treat disease. This year, I would like to highlight how NIDCR's investment in the basic sciences continues to yield important advances in oral and public health. I also would like to mention how NIDCR stands to benefit from the recently launched NIH Roadmap which has the potential to catalyze virtually all areas of oral health research and, most importantly, hasten the development of novel treatments that could greatly improve American oral health.

GENE TRANSFER AND THE SALIVARY GLANDS

A prime example of basic research creating new clinical opportunities is the transfer of replacement genes into the salivary glands for therapeutic purposes. In the early 1990s, a team of NIDCR scientists published their initial paper on the technical feasibility of this approach. Thereafter, they began a unique long-term research interest in transferring replacement genes into the salivary glands of persons with Sjögren's syndrome and cancer patients whose salivary glands were damaged during radiation treatment. The hope was that the replacement genes would increase the production of saliva and eliminate the chronic parched sensation that plagues people with dry mouth conditions.

The NIDCR scientists also began to apply their gene transfer studies to a third and seemingly less obvious therapeutic area: single-protein disorders, such as type I diabetes, human growth hormone deficiency, and erythropoietin-responsive deficiencies. Frequently overlooked in the medical literature, salivary glands not only release saliva into the mouth, they routinely secrete digestive enzymes and other proteins into the circulatory system. As the scientists later would demonstrate, the salivary glands readily accept gene-carrying vehicles, or vectors. Thereafter, with minimal coaxing, the salivary glands act as natural protein factories, dutifully manufacturing the encoded replacement protein and pumping it at steady levels into the circulation. The approach has some built in advantages over gene therapy in other

[6] Carmiel-Haggai M, Cederbaum AI, Nieto N. Binge ethanol exposure increases liver injury in obese rats. Gastroenterology, 125(6):1818–33. Dec. 2003.

parts of the body, such as the liver. Salivary glands are easily accessible and any potential adverse effects would be non-life threatening. Moreover, salivary gland cells are encapsulated to prevent leakage of the vector into the circulation and to other tissues.

Recently, the group developed a new version of gene-carrying vector that entered the salivary glands of mice and produced the human protein erythropoietin for at least one year, a major step forward in the research. Just as importantly, the vector—a stripped down, bioengineered version of the harmless adeno-associated virus—did not trigger a sustained immune response, a common setback in gene therapy experiments.

Building on this strong basic research base, NIDCR has developed a new initiative to evaluate the safety and efficacy of salivary gland gene transfer techniques in people with systemic single-protein deficiencies. The initiative will consist of three Phase I/II clinical trials. The first clinical trial will involve a prototype systemic single-protein deficiency disorder, adult growth hormone deficiency. As currently proposed, 21 patients will be enrolled in the study, which will be completed in four years. If successful, a second clinical trial will be conducted to treat people with erythropoietin-responsive deficiencies and ultimately a third clinical trial for those with Sjögren's syndrome and/or cancer patients with dry mouth.

PERIODONTAL DISEASE AND PRETERM BIRTH

Another outstanding example of basic research creating new clinical opportunities is in the area of preterm pregnancy. In the United States, about one in eight babies is born prematurely,[1] which is defined as a birth that occurs three or more weeks earlier than the expected due date. As all too many parents have tragically experienced, extremely preterm babies can be so small and underdeveloped that they must remain hospitalized for months and, if they survive, spend years battling chronic health problems.

This serious and common problem has spurred scientists to identify "risk factors" associated with premature births. These risk factors—which now include smoking, low-income status, hypertension, diabetes, alcohol use, genitourinary tract infections—allow doctors to identify women who are more likely to deliver prematurely and thereby tailor their prenatal care to control or eliminate the risk factors.

However, the list of risk factors remains a work in progress. An estimated one in four preterm births occur without any known explanation, and that has left scientists searching for additional susceptibility factors to help more mothers and reduce the estimated $13.6 billion per year spent in the United States on hospital stays for infants with a diagnosis of prematurity.[2]

In the mid 1980s, scientists began to suspect that periodontal disease might be one of these elusive risk factors. These NIDCR grantees and colleagues monitored women with more serious periodontal disease and found they were more likely to deliver early than those with mild or non-existent disease. They also have developed a plausible biological explanation to explain the possible association. Based on animal studies, the scientists hypothesized that certain bacteria from severe periodontal infections, most notably *Porphyroma gingivalis,* enter the bloodstream and eventually circulate to the womb. There, the oral pathogens colonize and irritate the uterine wall. This causes inflammation of the uterus and a rise in prostaglandins and other infection-signaling chemicals, which can induce early contractions and trigger premature labor.

Left unanswered is whether treating women for periodontal disease during pregnancy will help them give birth to full term babies. The NIDCR recently launched two large randomized clinical trials to answer this important public health question. These national studies, which merge the disciplines of dentistry and obstetrics, will involve over 2,600 women of various racial, ethnic, and economic backgrounds. What is unique about these clinical trials is there will be a yes-or-no outcome for each woman within 37 to 40 weeks, or the completion of the pregnancy. Women will not need to be tracked at great expense for 10 or 20 years to get the final answer, as is often the case in clinical research. Once all the data are compiled and analyzed, which could take an estimated five years to assemble and analyze, researchers anticipate that they will have sufficient clinical data to offer sound scientific advice one way or the other on this critical public health issue.

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[1] March of Dimes Defects Foundation. http://peristats.modimes.org. Access on March 15, 2003.
[2] March of Dimes, PeriStats.

PAIN RESEARCH

In another example of the potential payoff from basic research, scientists are mapping in greater detail the multiple routes, or pathways, that sensory signals travel en route to the spinal cord and brain. This work has resulted in several new leads in how to more effectively manage pain. One of the most promising new leads stems from work conducted at the NIDCR. Our scientists found that an ultrapotent compound selectively eliminated an entire class of pain-sensing neurons from the peripheral nervous system of a living organism. The compound, called resiniferatoxin (RTX), killed the neurons, blocking inflammatory pain, thermal pain sensation, and reducing hypersensitivity to pain. Importantly, the animals maintained their ability to sense pain, in this case from a pinch, and they remained well coordinated, an indication that RTX did not affect sensory nerves in the muscles and joints. Since these initial reports, the investigators have assembled additional preclinical data and are moving rapidly toward evaluating RTX in human clinical trials.

In order to seed additional discoveries in pain research and to help more Americans effectively manage pain, the NIDCR will begin an initiative to define the proteins and protein networks involved in processing pain-signal information in the orofacial region. This initiative encourages interdisciplinary studies that employ genomic and proteomic approaches, imaging technology, and computational biology to clarify the molecular events involved in chronic orofacial pain disorders.

PUTTING RESEARCH INTO PRACTICE

To achieve our goal of improved oral health for all people, NIDCR must ensure that research advances are translated and adopted into clinical practice. Many of the unique questions faced by dental health professionals on a daily basis are most appropriately addressed in dental practice settings, among unselected patient populations. Practice-based research networks can generate important and timely information to guide the delivery of health care and improve patient outcomes. The NIDCR will launch an initiative to create dental Practice-Based Research Networks (PBRNs) to conduct clinical research. In time, linking the oral health practice-based research networks with existing medical networks will provide additional patients, professional expertise, and integration of resources for conducting research across a broad spectrum of health care specialties. By connecting practitioners with experienced clinical investigators, PBRNs will enhance clinical research supported by the NIDCR and produce findings that are immediately relevant to practitioners and their patients. The networks can support a variety of clinical studies with clear and easily defined outcome measures, and they typically draw on the experience and insight of practicing clinicians to help identify and frame the questions. Because research is conducted in the real-world environment of dental practice, the results are more likely to be readily adopted by practitioners.

NIH ROADMAP

The NIH Roadmap provides several additional opportunities to the oral-health research community. For example the goals of the initiative *Building Blocks, Biological Pathways and Networks*—are closely linked to NIDCR's molecular anatomy efforts to identify the full complement of genes, proteins and protein networks that are expressed in both oral cancer and periodontal disease. Advances in proteomic analysis platforms will be crucial for NIDCR to achieve its goal of defining the salivary proteome—a critical step in the Institute's long-term goal to exploit the salivary secretions for diagnostic purposes. The *Molecular Libraries and Molecular Imaging* initiative holds great promise for accelerating NIDCR's progress in defining the molecular pathways of pain reception and in elucidating new therapeutic targets to manage chronic pain. In addition, the initiative *Research Teams of the Future* will enable NIDCR's ongoing inter- and multi-disciplinary efforts to further expand and develop new ways to approach research questions. Finally, the integration of dentists into the new clinical research infrastructure that will be created by the Roadmap is key given that overall health and oral health are interrelated and that certain systemic conditions such as diabetes, Sjögren's syndrome, HIV/AIDS and osteoporosis have important oral symptoms, manifestations or complications.

NIDCR envisions a clear path ahead for oral and craniofacial research. Many exciting new leads that have been reported in recent years makes it easy to imagine that the next wave of research advances will have a more profound and far reaching effect on oral health than ever before.

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

We have been joined by two members of the Appropriations Committee. Let me turn first to the distinguished chairman of the full committee, Senator Stevens.

Senator STEVENS. Well, Mr. Chairman, I am late. So I will just ask to put my statement in the record. I do greet our friends at the table and look forward to the comments and questions.

Senator SPECTER. Without objection, the statement will be made a part of the record.

[The statement follows:]

PREPARED STATEMENT OF SENATOR TED STEVENS

Thank you Mr. Chairman. It's a pleasure to welcome Dr. Zerhouni and his distinguished colleagues who head up the Institutes at NIH here today.

I'd also like to thank Dr. Andy von Eschenbach. Andy, I understand from my good friend Dr. Mike Phelps that you gave an excellent speech this past Sunday to the Academy of Molecular Imaging meeting in Orlando. As you know, PET and Molecular Imaging are special interests of mine.

I must be brief since I have three other hearings where I must make an appearance. However, I want to commend Dr. Zerhouni for his efforts to develop the "Roadmap" initiative.

That initiative aims to focus NIH's resources on several broad categories of medical research and to bring together different disciplines to make real, rapid and visible progress to determine the true basis of many diseases and then to treat them. The Roadmap, with its focus in the Director's office is important because no single NIH Institute can address these problems alone.

I'm particularly pleased that you have chosen to focus early efforts of the Roadmap on the integration of nanotechnology, systems biology, and molecular imaging. By combining these three disciplines we hope to discover the molecular basis of diseases like cancers and then to develop targeted molecular therapies to arrest the progress of the disease and cure it.

In the fiscal year 2004 appropriations legislation I sponsored an amendment to give the Director of NIH new authority to put together innovative collaborative approaches to medical research to help speed up the process. I hope that you, Dr. Zerhouni, will use that authority to take bold and visionary steps to help us find these cures.

I've been a longtime supporter of large increases in funding for medical research. I continue that support, but I must warn you that it will be more and more difficult to sustain increases for medical research unless you do pursue bold new approaches such as nanosystems biology that have the potential to show real results that the American taxpayer can see. We must begin to show a return on our investment in order to continue it.

Once again, I commend Dr. Zerhouni and the directors of the NIH Institutes for their leadership and efforts on behalf of all people.

Senator SPECTER. Senator Cochran, do you have an opening statement?

OPENING STATEMENT OF SENATOR THAD COCHRAN

Senator COCHRAN. Mr. Chairman, thank you very much. I have submitted a statement as well and hope it will be included in the record.

I want to commend the Director and his associates who are here today for the fine work that you are doing. I am particularly impressed with the work in health disparities and some of the research that is being undertaken now and funded by the National Institutes of Health.

PREPARED STATEMENT

I notice an increase in the budget request for the National Center for Minority Health and Health Disparities. I think that is the entity that is supporting the Jackson Heart Study in my State

where very meaningful work is being done in conjunction with the University of Mississippi Medical Center and Jackson State University and other educational institutions in our State to try to get at the bottom of some of the questions of why there is such a disparity in some kinds of heart diseases. This is being done in conjunction with the National Heart, Lung, and Blood Institute as well. But I think the need for more research, conducted in the places where we are experiencing health disparities or high incidences of chronic diseases, is something that is overdue, and I congratulate you for taking this initiative.

[The statement follows:]

PREPARED STATEMENT OF SENATOR THAD COCHRAN

Dr. Zerhouni, thank you for joining us today to discuss the budget for the National Institutes of Health. We have had great success in increasing NIH funding. It is my hope that we continue to support high quality research, and focus this research on the most pressing health issues of our country. Our goal should be to make sure NIH research benefits all Americans.

I know you are familiar with the Jackson Heart Study, which looks at the reasons why African-Americans suffer disproportionately from heart disease. I hope the NIH will continue to take an active role in making sure research like this reaches underserved areas of our country. This relatively small investment has made a tremendous impact on my state. I am encouraged by the progress made by institutes, like the National Center for Minority Health and Health Disparities. I am pleased to support NIH in these efforts.

Senator SPECTER. Thank you, Senator Cochran.

We will now proceed with 5-minute rounds of questioning, as is the custom of the subcommittee.

FISCAL YEAR 2005 BUDGET REQUEST

Dr. Zerhouni, your proposed budget will permit grant increases by only 1.3 percent instead of the inflationary increase of 3.5 percent. If NIH applied its usual policy of providing an average grant increase equal to the rate of inflation, it is my understanding that about 640 fewer competing grants would be funded than in 2004.

First of all, is that accurate?

Dr. ZERHOUNI. That is accurate, Senator.

Senator SPECTER. After the increases which we have provided over the last 5 years, do you think the proposed budget is sufficient to maintain the momentum and bring discoveries from the laboratory to the doctor's office?

A subset of that is, how much additional funding would be required to restore the usual NIH average cost policy, assuming the same number of grants which are now in the budget?

Dr. ZERHOUNI. Ideally, Mr. Chairman, you would like to be sure not to fall behind inflation. However, this year, because of the very difficult budget environment, we had to make some difficult choices. We elected to maintain the number of grants to be able to provide as many scientists the opportunity to succeed in applying and made some sacrifices on the cost increases.

If we had $220 million more—the number is $220 million—we could satisfy both conditions: have enough grants and inflationary increases.

Senator SPECTER. If the Congress is willing to appropriate the additional $1.3 billion, what new research initiatives would NIH be able to conduct with these additional funds?

Dr. ZERHOUNI. As you know, because of the doubling and the opportunities offered by the doubling, many of our institutes, if not all of them, have opportunities in translation in clinical research. This is the area of research generally that is difficult to undertake in a budget that is the budget that we are requesting.

So when you look at the priorities that we would have to fulfill, if we had more resources, the first one would be to keep up with inflation. The second would be to continue our analysis and the framework for the Roadmap for medical research, accelerate that. We have some programs like the extramural construction programs, the IDeA program, that we would like to enhance over time, including training stipends. But the most important report from all the institutes is that there are some clinical trials in translational research that will have to be slowed down.

Senator SPECTER. Well, I would like to have a more detailed answer for the record on what the impact will be on the administration's request contrasted with what the impact would be on an additional $1.3 billion. So we have specific information as to how many grants there would be, what will happen to the clinical programs.

Let me turn now to the issue of stem cell research. You and I have discussed this at some length and the President made his famous statement back on August 9th of 2001 about certain stem cell lines being added. Some of those stem cell lines are contaminated with mouse feeder cells. Some of those stem cell lines are owned other places. We see Harvard with a $100 million allocation, which is wonderful but nothing compared to the $28 billion you have. We see South Korea taking the lead. We see scientists leaving the United States because ideology is conflicting with medical research.

[The information follows:]

RESEARCH THAT NIH COULD FUND WITH AN ADDITIONAL $1.3 BILLION

The fiscal year 2005 President's Budget requests an additional $764 million for NIH, a significant increase to the program level given the competing priorities within the Federal budget. An additional $1.3 billion over the request would provide $30.057 billion, an increase of 7.2 percent over fiscal year 2004. With this additional funding, NIH would fund a larger share of the great research ideas that scientists submit to us. We would be able to fund about 700 more research project grants, increasing chances of a scientist's application being funded and increasing the currently expected "success rate" from the 27 percent in the President's Budget to 29 percent. Additional priorities would include:

—Accelerating implementation of Roadmap initiatives;
—Implementing an interdisciplinary approach to neuroscience research by completing the phase 2 of the Porter Neurosciences Building;
—Providing average cost increases equal to biomedical inflation and finance the committed levels for competing continuation grants;
—Increasing support for research training awards; and
—Increasing the amounts NIH pays on career awards.

Examples of the new research initiatives and significant expansions of ongoing programs that NIH would conduct with these additional funds follow:

TRANSDISCIPLINARY RESEARCH ON ENERGETICS AND CANCER (TREC) (NCI)

—Novel initiative involving scientists from multiple disciplines and encompassing projects spanning the biology and genetics of energy balance to behavioral, sociocultural, and environmental influences upon nutrition, physical activity, weight, energy balance and energetics.
—The TREC Centers would foster collaboration among transdisciplinary teams of scientists with the goal of accelerating progress towards reducing cancer inci-

dence, morbidity and mortality associated with obesity, low levels of physical activity and poor diet.
—Centers would also provide training opportunities for new and established scientists who can carry out integrative research on energetics, energy balance and its consequences.

CANCER BIOMEDICAL INFORMATICS GRID (CABIG) (NCI)

—Cancer research platform with common standards to expedite progress by creating a network that links organizations, institutions, and individuals to enable the sharing of cancer research infrastructure, data, and tools.
—All cancer researchers would have access to a common research infrastructure that creates a plethora of opportunities to not only make important new findings but to do so more quickly and efficiently than ever before.
—This new system would offer a library of tools and resources—from clinical trial management systems to tissue bank and pathology tools—that are all built to common standards and are interoperable with other existing systems.
—Study population data would be far more robust and researchers will be able to mine data in a way that simply isn't possible at the moment.
—Joins the various fields of cancer research—from etiologic research to prevention, early detection and treatment.

UNDERSTUDIED CANCERS OF HIGH LETHALITY (NCI)

—A key element to the elimination of death from cancer by 2015 would be to focus on malignancies which are highly fatal, such as pancreatic, esophageal, and liver cancers.
—When these cancers are found, relatively little prolonging of life or quality of life follows.
—Understanding gene-environment interactions is important in learning who is at elevated risk, and how that risk is regulated.
—Discoveries in these areas would lead to more accurate and cost-effective public health interventions aimed at eliminating mortality.

PATIENT NAVIGATION RESEARCH PROGRAM: ELIMINATING BARRIERS TO TIMELY DELIVERY OF CANCER DIAGNOSIS AND TREATMENT SERVICES (NCI)

—A major disconnect or gap exists between cancer *Discovery* and *Development* research and *Delivery* for many Americans. *Discovery* and *Development* research results in beneficial procedures for cancer prevention, early detection, diagnosis, and treatment that are intended for all Americans. Health disparities arise when the *Delivery* system does not provide access to timely, standard cancer care to everyone in the nation. NCI has established the goal of eliminating suffering and death due to cancer by 2015.
—The NCI is challenging principal investigators to develop effective patient navigation interventions. These interventions would address access barriers to quality, standard cancer care. The purpose of the *Patient Navigation Research Program* (PNRP) would be to develop interventions to reduce the time to delivery of standard cancer care services after identifying a cancer-related abnormal finding.
—The patient navigator could assist patients and their families through the cancer care continuum.
—The research hypotheses are that navigated patients would: (1) receive timelier, definitive diagnosis following screening and abnormal finding; (2) receive more timely treatment following positive diagnosis; (3) improve their satisfaction with the health care system experience.

STUDY TO IDENTIFY RISK FACTORS FOR CORONARY HEART DISEASE (CHD) IN HISPANIC POPULATIONS (NHLBI)

—The nation's largest minority group.
—Involve four community-based cohorts of adults, one each of majority Cuban, Puerto Rican, Mexican American, and Central American origin.
—Examine the role of acculturation in the development of risk factors and determine if any play a uniquely harmful role in the development of CHD in Hispanics.
—Include a closely integrated community and professional education component to return the benefits of research results to the participating communities.

FIVE-YEAR RANDOMIZED CLINICAL TRIAL OF CHRONIC OXYGEN USE IN MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PATIENTS (NHLBI)

—COPD is the fourth most common cause of death in the United States.
—Oxygen therapy is known to extend the life of patients with severe COPD and hypoxemia.
—Billions of dollars are spent in the United States each year to provide oxygen for patients with moderate or severe COPD without good evidence as to who benefits.
—The trial would determine the effects of oxygen therapy on life expectancy, hospitalization rates, independent living, and quality of life.

MULTI-CENTER CLINICAL TRIAL TO EVALUATE NEW TREATMENT APPROACHES FOR SARCOIDOSIS (NHLBI)

—Sacroidosis is a multisystem disease that usually affects the lungs, and is more common in black Americans.
—Current treatment, which is based mainly on corticosteroids and cytotoxic agents, is non-specific and has many dangerous side effects.
—An NHLBI Sarcoidosis Research Working Group and several patient advocacy groups recommended support for a trial to test new agents for sarcoidosis.

IDENTIFY AND TEST APPROACHES TO REDUCING CARDIOVASCULAR DISEASE THAT ARE SPECIFIC TO AMERICAN INDIAN AND ALASKA NATIVE POPULATIONS (NHLBI)

—Such an initiative would test approaches to reducing cardiovascular disease (CVD) risk factors in American Indian/Alaska Native (AI/AN) populations that can be incorporated into clinical programs of community health care systems or delivered through other public health approaches in native communities.
—Many AI/AN communities bear a heavy burden of CVD and modifiable CVD risk factors.
—AI/AN communities are concerned that few intervention studies have been launched to test possible solutions.

PRACTICE BASED RESEARCH NETWORKS OF DENTAL SPECIALISTS (NIDCR)

—NIDCR's Practice Based Research Networks (PBRN) initiative would otherwise be limited to networks of general dental practitioners.
—Networks provide an infrastructure for conducting multiple, collaborative clinical trials and observational studies relating to dental practice and oral health care.
—Linkage of the oral health PBRNs with existing medical PBRNs would provide additional patients, professional expertise, and integration of resources for conducting clinical research across a broad spectrum of health care specialties.

REGENERATIVE DENTAL MEDICINE (NIDCR)

—Diseases and injuries that damage orofacial tissues have a serious impact on quality of life.
—Human stem cells would be utilized in combination with new bio-inspired materials to regenerate the complex structures of the orofacial system.
—Researchers would develop and test a number of stem cells and biomaterial structures that mimic the multi-dimensional architecture/function of tooth structures.

PROSPECTIVE STUDIES ON CRANIOFACIAL PAIN & DYSFUNCTION (NIDCR)

—Participants enrolled in this study would be followed over time to identify risk factors associated with or predictive of the onset of craniofacial pain and dysfunction.
—Temporomandibular joint (TMJ) dysfunction is a condition of particular interest.

CLINICAL RESEARCH TRAINING (NIDCR)

—In the "post-genomic era," translational and clinical research plays an important role in bringing laboratory observations into the clinical setting.
—NIDCR's new program announcement would foster clinical research training in multidisciplinary research settings for all members of the clinical research team.

FULL-SCALE CLINICAL TRIAL OF PRIMARY INTERVENTIONS TO PREVENT OR DELAY TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS (NIDDK)

—Cases of type 2 diabetes are increasing in the pediatric population, especially among adolescents and in certain minority groups.
—A school-based intervention approach may be an effective way to prevent risk factors for type 2 diabetes in children and adolescents.
—Pilot studies for a multi-site, multi-component, school-based intervention trial employing both environmental and behavioral changes are under way; could launch the trial in fiscal year 2005.

IMPROVE CLINICAL TRIALS FOR TREATMENT OF INFLAMMATORY BOWEL DISEASE (IBD) (NIDDK)

—The conduct of new clinical trials in IBD is hampered by the current need to rely on indirect diagnostic tests and nonspecific clinical features.
—The conduct of clinical trials and development of safer, more effective treatments would be accelerated by research in proteomics, to discover new biomarkers, and in molecular imaging, to discover new non-invasive diagnostic imaging tests.

STUDY THE ROLE OF THE INTRAUTERINE AND POSTNATAL ENVIRONMENTS IN THE DEVELOPMENT OF OBESITY (NIDDK)

—A better understanding of aspects of the intrauterine environment and a mother's medical status that contribute to future overweight and obesity in offspring could lead to more effective interventions before, during, or shortly after pregnancy.
—Strategies to prevent or treat obesity could also greatly benefit from research on the impact of diet and other environmental factors on the early development of brain pathways regulating calorie intake and energy expenditure, and the permanence of these effects in adulthood.
—Tools are available to conduct these studies in appropriate animal models, including primates.

EXPAND FEASIBILITY TRIAL OF DAILY DIALYSIS TO DETERMINE EFFECTS OF NEW, MORE INTENSIVE DIALYSIS MODALITIES ON MORTALITY AND CARDIOVASCULAR DISEASE (NIDDK)

—Clinical studies are needed to determine whether life expectancy of persons with end-stage renal disease (ESRD), or chronic kidney failure, can be improved by modifying standard dialysis regimens.
—Clinical centers have been established to test the feasibility of a randomized clinical trial of more frequent dialysis.
—The current frequent dialysis trial is limited by size and design to measuring intermediate outcomes, such as blood pressure, anemia, and quality-of-life.
—An expansion of the trial could enable assessment of the effect(s) of any change in dialysis regimen on hospitalization rate and mortality, and on cardiovascular events—e.g., stroke, myocardial infarction and heart failure—which often complicate ESRD.

INITIATE THE VERY LARGE PHASE III CLINICAL TRIALS FOR PARKINSON'S DISEASE (NINDS)

—Necessary to adequately test one or more of the neuroprotective drugs for Parkinson's disease (minocycline, creatine, coenzyme Q10 and GPI–1485) that are being tested in pilot trials.

CONDUCT A PHASE III CLINICAL TRIAL OF CEPHALOSPORIN FOR THE TREATMENT OF ALS (LOU GEHRIG'S DISEASE) (NINDS)

—A screen of 1,040 drugs for potential use against neurodegenerative diseases revealed one that may be particularly helpful for ALS—the antibiotic cephalosporin.

LAUNCH CHEMICAL COUNTERTERRORISM RESEARCH TO COMBAT NERVE AGENTS (NINDS)

—A number of chemical agents and toxins that have served or could serve as terrorist weapons that target the nervous system.
—Research initiatives would focus on ameliorating the acute neurologic responses to these chemical weapons as well as alleviating any chronic neurodegenerative effects.

EXPAND THE SPECIALIZED PROGRAMS OF TRANSLATIONAL RESEARCH IN ACUTE STROKE (SPOTRIAS) (NINDS)

—From four to eight centers.
—Would accelerate translation of basic research findings into clinical practice in acute ischemic and hemorrhagic stroke.

INITIATIVE FOR PANDEMIC INFLUENZA (NIAID)

—Accelerate the development of next generation influenza antiviral drugs and the production and clinical testing of up to four pilot lots of candidate vaccines by up to one year or more.
—Influenza routinely causes 36,000 deaths per year in the United States; however, the ability of flu viruses to occasionally jump from animals to humans poses an imminent threat of a pandemic affecting millions of people—over 20 million people worldwide is estimated to have died during the flu pandemic of 1918.
—Research would also expand surveillance of emerging flu strains in Asian animals to support development of new vaccines against influenza strains with pandemic potential.

CLINICAL TRIALS OF HIV/AIDS VACCINE CANDIDATES (NIAID)

—Expand clinical trials to accelerate by one or more years clinical evaluation of six promising HIV vaccine candidates.
—Forty million people were estimated to have HIV/AIDS as of December 2003, with five million new infections occurring in 2003. Another three million people died of the AIDS pandemic in 2003, including 500,000 children, with a total of 70 million people projected to die of the disease by 2020 if the current trends continue.
—As with other pandemic infectious diseases, a key component to preventing the spread of HIV/AIDS, and to mitigating the long-range impact of the AIDS pandemic, is the development of an effective HIV/AIDS vaccine. Critical challenges to developing an effective vaccine include the need to clinically evaluate a large number of promising HIV vaccine candidates in humans as rapidly as possible to determine the toxicity and effectiveness of the vaccine candidates. Factors contributing to the need to clinically evaluate a large number of the most promising vaccine candidates include the multitude of different HIV/AID virus strains in existence and the frequency at which the virus mutates and the fact that the virus infects and destroys the immune system.

CLINICAL TRIALS IN ORGAN TRANSPLANTATION (NIAID)

—Expand and accelerate clinical trials to develop therapeutic strategies to reduce the immune-mediated morbidity and mortality of organ transplantation.
—Over 25,000 people receive organ transplants each year. Although the one-year survival for single-organ transplantation has improved over the last 15 years to a level approaching or exceeding 90 percent, there has been little success in reversing the decline in long-term graft-vs-host disease and patient survival (13 percent to 55 percent at 10 years, dependant upon organ).
—Studies would support both children and adults and will address the barriers to short- and long-term success of transplant procedures, including incompatibility between donor and recipient, acute and chronic rejection, and complications of long-term pharmacologic immune suppression.

CLINICAL TRIALS OF TOPICAL MICROBICIDES (NIAID)

—Expand existing support of clinical trials to accelerate the clinical evaluation of four promising microbicide candidates that have unique mechanisms of action to potentially protect against sexually transmitted diseases (STD), including HIV/AIDS.
—Topical microbicides are creams, gels or foams that can be applied to the vagina or rectum and prevent STD-causing microbes, including HIV, from invading the host. Pharmaceutical companies have been reluctant to invest in research on microbicides primarily because not enough data has been gathered through large clinical studies in humans to provide a "proof of concept" of any microbicide product.
—A partially effective microbicide could avert more than 2 million HIV infections over a 3-year span; also, microbicides could play a critical role in reducing STD transmission from mother to infant during childbirth.

DETERMINE THREE-DIMENSIONAL STRUCTURES OF PROTEINS (NIGMS)

—Partner with other Institutes.
—Includes those related to cancer and emerging infectious diseases.
—Would be useful for the design of new antibiotics or anti-cancer agents.

RESEARCH RELATED TO DETERMINING WHY DIFFERENT INDIVIDUALS RESPOND DIFFERENTLY UPON TREATMENT WITH THE SAME DRUGS (NIGMS)

—Would help physicians customize treatment to individual patients and may guide the development of new drugs that are more predictively effective in most people.

DEVELOPMENT OF TOOLS FOR INVESTIGATING MODEL ORGANISMS (NIGMS)

—Model organisms such as fruit flies, mice, and roundworms have provided great insights into fundamental biological mechanisms and into human disease.

INNOVATIVE METHODS OF NEWBORN SCREENING (NICHD)

—While ensuring protection of privacy and providing ethical safeguards, the NIH could proceed with efforts to identify, at birth, hundreds of genetic defects associated with mental retardation, primary immunodeficiency diseases, and other potentially disabling and fatal conditions.
—Technologies generated by the Human Genome Project are available to screen for hundreds of genetic diseases in newborns.
—A database in rare genetic diseases could be developed to enable scientists to identify unrecognized genetic defects in newborns, to study currently untreatable disorders, and to develop new therapeutics.
—New screening techniques could allow clinical and preventive interventions for currently treatable genetic disorders, such as Severe Combined Immunodeficiency Disease (SCID), in time to prevent or mitigate risks of early death or life-long disability.

GENOMIC AND PROTEOMIC RESOURCES FOR PREMATURE BIRTH (NICHD)

—The NIH could establish a major consortium to create high-quality data on human gene and protein expression, and to make this information available on a publicly-accessible database that will be dedicated to prematurity research. Investigators could mine the database to advance their own research into the causes of and ways to prevent premature birth.
—Premature birth causes almost 70 percent of neonatal deaths and reducing prematurity would reduce wide racial disparities in infant mortality.
—The depth and accessibility of the new genomic and proteomic database could enable scientists to discover biomarkers for premature birth and ultimately to develop early diagnostic and effective treatment interventions.

RESEARCH BASE TO ASSESS EARLY CHILDHOOD LEARNING AND SCHOOL READINESS (NICHD)

—The NIH could develop, refine, validate, and scale-up tests to assess how well preschool programs help young children—especially those at risk of school failure—to achieve "school readiness," cognitively, socially, and behaviorally.
—Significant academic, public, and political attention is focused on the educational achievement of all children, beginning with preschoolers, with certain federal funds tied to school systems' performance.
—Preschool programs need scientifically-based tests to measure accurately how well they prepare young children for later school success. The programs especially need tests to measure their performance with non-English speaking, ethnically diverse, and educationally at-risk preschoolers. For the most part, such tests do not exist, leaving preschool programs unable to measure their performance for purposes of federal funding.
—The NIH is the primary research agency with the basic and applied scientific expertise to produce these tests, which are now lacking.

THE NATIONAL CHILDREN'S STUDY (NICHD)

—The first two vanguard centers could be established for this ground-breaking, congressionally-authorized, longitudinal study of children's health and development. (There would be significantly larger out-year costs.)

—Extensive planning and selected feasibility studies enable vanguard centers, for this large and complex research effort, to investigate how environmental factors, broadly defined, may influence children's health and development.
—Primary care pediatric practices and other types of clinical sites could become vanguard sites.

NEW INTERVENTIONS TO IMPROVE PREGNANCY OUTCOMES (NICHD)

—The NIH could proceed with clinical trials and related studies to prevent preterm births and improve neonatal outcomes.
—An NIH research network recently discovered the first effective intervention—progesterone treatment of high-risk women during pregnancy—to prevent recurrent preterm birth. The new treatment cannot be approved by the FDA until researchers study children of mothers who received the experimental treatment to detect any later-emerging adverse effect in the children.
—A clinical trial is needed to affirm preliminary findings that a nutritional supplement during pregnancy (an Omega-3 (n-3) polyunsaturated fatty acid) is particularly efficacious in preventing recurrent preterm birth in African American women, for whom the experimental progesterone treatment was less effective.
—A clinical trial is needed to affirm preliminary findings that a single, simple injection of tin mesoporphyrin can successfully prevent complications of hyperbilirubinemia that can result in severe, life-long disabilities. If not diagnosed and treated, hyperbilirubinemia can lead to jaundice, brain injury and kernicterus (a condition of severe neural symptoms, associated with high levels of bilirubin in the blood).

CLINICAL TRIAL FOR THE TREATMENT OF INFLAMMATORY EYE DISEASE (NEI)

—Would be able to begin a clinical trial to evaluate a treatment for uveitis that will greatly enhance patients' quality of life.
—Uveitis is a group of ocular inflammatory disorders that represent a major cause of vision loss and blindness in the United States.
—This new monoclonal antibody therapy could mean fewer side effects than current therapies that require systemic, immuno-suppressive drugs, leading to an improved quality of life.

CLINICAL TRIALS NETWORK FOR THE TREATMENT OF AGE RELATED MACULAR DEGENERATION (AMD) (NEI)

—Could launch a clinical trials network to test promising new therapies for age-related macular degeneration.
—A clinical trials network is needed to test a variety of new treatment approaches targeting the full range of disease forms and levels of severity of age-related macular degeneration.
—Age-related macular degeneration is the leading cause of vision loss among Americans over 65 years of age, the fastest growing segment of the U.S. population.

ROBUST PROGRAM TO EVALUATE THE TOXICOLOGY OF NANOSCALE MATERIALS (NIEHS)

—Nanoscale materials are already appearing in commerce as industrial and consumer products and as novel drug delivery formulations. Commercial applications and resultant opportunities for human exposure may differ substantially for nanoscale vs. "bulk" materials.
—Currently there is very little research focus on the toxicology of manufactured nanomaterials. There are indications in the literature that manufactured nanomaterials may distribute in the body in unpredictable ways and that certain nanoparticles have been observed to preferentially accumulate in particular organelles.
—The NTP/NIEHS research program would evaluate the toxicological properties of major nanomaterials classes which represent a cross-section of composition, size, surface coatings, and physico-chemical properties, and use these as model systems to investigate fundamental questions concerning if and how nanomaterials can interact with biological systems.

USE OF METABOLOMICS TECHNOLOGIES FOR PREDICTING TOXICOLOGICAL RESPONSES (NIEHS)

—Assessment of exposure and of risks from exposure could be greatly improved by using metabolic indicators such as changes in gene, protein or metabolite expression.

—Research supported by this initiative would focus on the application of metabolomics technologies to identify predictive markers of exposure, toxicity and disease in animal and human populations; link metabolic profiles with biological pathways and mechanisms of environmentally-related exposures and diseases; and develop computational and modeling approaches for assessment and integration of metabolomics data in predictive toxicology research.
—This program would be a critically important application of the basic methodology development work being undertaken as part of the NIH Roadmap initiative on Metabolomics Technology Development.

PREVENTION TRIALS TO ASSESS THE POTENTIAL ABILITY OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND A COMBINATION OF ANTI-OXIDANT VITAMINS (NIA)

—Prevent Alzheimer's disease and age-associated cognitive decline.

DEVELOPMENT OF A CLINICAL TRIALS CONSORTIUM (NIA)

—Test testosterone therapy for older men with low testosterone levels who experience weakness, frailty, or a specific disability that may be related to low testosterone.

NEW INTERVENTIONS FOR PREVENTION AND CONTROL OF HEART FAILURE IN PERSONS AGED 65 AND OLDER (NIA)

—Fully develop and validate new interventions through clinical trials.

MULTIDISCIPLINARY IMAGING RESEARCH PARTNERSHIPS FOR ADDRESSING IMPORTANT BIOLOGICAL OR MEDICAL RESEARCH PROBLEMS OF SKELETAL MUSCLE AND ASSOCIATED SOFT TISSUE (NIAMS)

—Improved imaging techniques provide a non-invasive way to monitor changes in muscle (including muscular dystrophy and other muscle diseases) and soft tissue.
—Multidisciplinary imaging research partnerships would stimulate the development of novel imaging technologies that will help us understand the genetic and molecular bases of musculoskeletal soft tissue function, disease, and injury processes.
—Improved visualization of skeletal muscle and associated soft tissue would enable researchers to more accurately measure change during treatment or recovery from injury.

PURSUE THE RESEARCH NEEDS AND OPPORTUNITIES IDENTIFIED AT THE RECENT NIH CONSENSUS DEVELOPMENT CONFERENCE ON TOTAL KNEE REPLACEMENT (NIAMS)

—Approximately 300,000 total knee replacements are performed each year in the United States for end-stage arthritis of the knee joint, and the rate of total knee replacement procedures increases each year.
—While these replacements have shown outstanding success, controversies still exist regarding implant designs and treatment. Research studies suggest that there are particular challenges that must be addressed in patients with Parkinson's disease, rheumatoid arthritis, and diabetes mellitus, as well as total knee replacements in younger patients.

INCREASE SUPPORT FOR TRANSLATIONAL RESEARCH—MAXIMIZING THE RESULTS OF BASIC RESEARCH TO IMPROVE PUBLIC HEALTH (NIAMS)

—To enhance and expand translational research, a new centers program is currently being or would be created called centers of research translation.
—These centers would pair basic and clinical projects in investigator-initiated and directed research that is centered around particular diseases. Different diseases might require different translation mechanisms and strategies.
—The goal of the centers is the application of powerful tools and knowledge from basic research to clinical research to improve human health.

ADDITIONAL STUDIES ON INNOVATIVE THERAPIES FOR RHEUMATIC AND SKIN DISEASES (NIAMS)

—Would expand a successful program that the NIAMS instituted in fiscal year 1999.
—Would solicit investigator-initiated proposals for clinical trials of innovative therapies or approaches for the treatment of rheumatic and skin disease.

—The previous program has produced a number of ongoing clinical trials that form the cornerstone of NIAMS-funded trials in rheumatic diseases.
—It is anticipated that the trials may identify new therapies for rheumatic and skin diseases.

OTITIS MEDIA (NIDCD)

—Would initiate Phase One trials of vaccine candidates.

INITIATE A DEFINITIVE EPIDEMIOLOGICAL STUDY (NIDCD)

—Would establish the role of prenatal exposure to cytomegalovirus in progressive hearing loss during childhood.

COMMUNICATION DISORDERS (NIDCD)

—Would expand research to identify the hereditary basis.

HAIR CELL DEGENERATION AND REGENERATION IN THE INNER EAR (NIDCD)

—Would initiate new research to define the molecular basis.

ENHANCE CAPACITY FOR DISASTER/TERRORISM MENTAL HEALTH RESEARCH (NIMH)

—Could enlarge this currently small program to establish emergency research protocols in conjunction with local public health authorities and develop critically needed measures for use in emergency/disaster research studies.

RESEARCH INITIATIVE ON PEDIATRIC BRAIN-BEHAVIOR DEVELOPMENT VITAL TO DIAGNOSING AND TREATING CHILD MENTAL DISORDERS (NIMH)

—This initiative would result in the first-ever identification of neuroimaging markers of specific child mental disorders which will lead to improved diagnostics and potential for new treatments in pediatric mental illnesses.

USE NIMH CLINICAL TRIAL NETWORKS TO LAUNCH TRIALS ON SIMULTANEOUS USE OF MULTIPLE PSYCHIATRIC MEDICATIONS FOR THE SEVERELY MENTALLY ILL (NIMH)

—Multiple medications is a widespread practice, but there is limited scientific data about its health effects and implications.

ANOREXIA AND BULIMIA (NIMH)

—Would expand research on understanding eating disorders.

MORE RESEARCH USING BRAIN IMAGING TECHNIQUES (NIDA)

—Would study how exposure to drugs of abuse can affect the developing human brain.
—Understanding precisely how brain changes relate to behavior, especially during childhood and adolescence, is critical to designing effective strategies for reducing drug use in the United States.
—Better treatment strategies targeting children and adolescents would be developed through these efforts.

COLLABORATIONS OF ESTABLISHED CLINICAL TRIALS NETWORK (CTN) WITH OTHER ESTABLISHED NETWORKS AT NIH (NIDA)

—NIDA CTN staff and staff from NCI's Community Clinical Oncology Program have discussed the possibility of jointly supporting a smoking cessation study. This study would bring these two NIH clinical research networks together in a synergistic collaboration and test the networks' interoperability.
—CTN has also had discussions with NICHD to link the CTN to a Network at NICHD that is studying adolescents and comorbidity.

ENHANCE OUR UNDERSTANDING OF THE GENETIC OR HERITABLE RISK FACTORS ASSOCIATED WITH DRUG ABUSE USING THE CTN AS A VALUABLE RESOURCE (NIDA)

—The CTN could serve as a resource to acquire genetic information on participants in clinical trials and to better characterize different phenotypes associated with addiction.
—As gene variants are identified in association with drug addiction, research could be conducted to determine how this genetic information can be used to tailor medications to an individual's genetic needs. This knowledge could be incorporated into ongoing medications trials in the CTN.

EXPAND RESEARCH ON PREVENTING DRINKING BY YOUTH IN RURAL/SMALL URBAN AREAS (NIAAA)

—Note: Partnerships have been formed with academic health centers, abbreviated "AHC," to conduct this research. AHC have in place the disciplines required, as well as extensive service networks in rural and small urban regions.
—Would expand the number of AHC sites that would conduct the research.
—Would collect data on psychological and physical development, and environmental/community circumstances, that are not routinely collected in medical settings. A variety of biomedical, psychosocial, and environmental factors act in concert to lead to adverse outcomes, such as alcohol-related problems. We must understand what all of these factors are and how they interact, if we are to make real advances in preventing and treating adverse outcomes of alcohol use among youth.

EXPAND RESEARCH AIMED AT DEVELOPING MEDICATIONS FOR ALCOHOLISM (NIAAA)

—Would develop animal models of response to alcohol that closely predict efficacy of compounds to be tested in humans.
—Would create a clinical-trials network for early Phase II human trials. These trials could yield relatively quick results and can indicate which compounds are worth the resources required for IND approval and Phase III trials. Partnerships would be sought with pharmaceutical companies interested in compounds found to be successful in NIAAA early Phase II human trials.

EXPAND RESEARCH ON ALCOHOL METABOLISM (NIAAA)

—Alcohol metabolism plays a crucial role in alcohol dependence and in alcohol-induced organ damage.
—Would form a bioinformatics data base, including data on gene expression, proteomics, and metabolomics involved in alcohol metabolism. This would be very important to our understanding of which genes and proteins are involved in addictive behavior and alcohol-induced organ damage, including cancer.
—In human clinical studies, use metabolomics and proteomics to generate information on biomarkers of early/late tissue damage, and identify targets for medication development.
—Using imaging technology, would determine if alcohol metabolism occurs in the brain and, if so, determine what enzymes are involved.
—Would identify all adducts (especially those that promote autoimmune reactions) that result from alcohol metabolism, and their roles in addictive behavior and organ damage.
—Would understand the interactions of alcohol metabolism with comorbid conditions, such as obesity and diabetes.

TISSUE ENGINEERED HUMAN MODEL SYSTEMS (NIBIB)

—Would stimulate research and development in three-dimensional human tissue model systems; engineered tissues for drug development; and cell-based sensors for clinical diagnosis and treatment.
—Tissue engineering holds the promise to repair and/or replace damaged organs.
—Tissue engineering strategies focusing on cell-based therapies, or treatment modalities that rely on cells as the agents for the treatment of diseases, have the potential to revolutionize human therapeutics in the 21st century.

MINIMALLY-INVASIVE, IMAGE-GUIDED SURGERY (NIBIB)

—Would support research needed to rapidly develop computer-assisted, image-guided microsurgery, which could replace traditional surgery.
—Image-guided, minimally-invasive surgical procedures involve less patient risk and pain and result in reduced hospital stays and shorter recovery periods.
—Advances in surgical robots and microsurgical techniques could enhance a surgeon's ability to perform complex tasks that cannot be performed by hand.
—Could support: integration of existing technologies and development of new technologies to navigate human anatomy, obtain diagnostic tissues, localize and treat human disease and injury, and monitor responses to surgical interventions.

CHEMISTRY OF IMAGING AGENTS AND MOLECULAR PROBES (NIBIB)

—Could support exploratory projects for the synthesis, physical characterization, and initial demonstration of feasibility for clinical imaging agents for physiological, anatomical, and molecular imaging.
—The ability to image molecular processes and cell function in vivo provides an opportunity to understand biological processes as they occur in their environment.
—Knowledge gained may be used to advance early-stage disease detection and individually-tailored therapeutic interventions.
—The development of new clinical imaging agents requires focused efforts by chemists and molecular biologists to discover new compounds and materials suitable for in vivo imaging.

BRAIN-COMMUNICATION INTERFACE (NIBIB)

—Could develop technologies to create a more functional and convenient system for restoring movement to paralyzed individuals.
—Investigators have been successful in making Function Electrical Stimulation (FES) a practical solution for restoring some movement to paralyzed individuals.
—Current systems allow individuals with spinal cord injuries to stand and breathe, and can restore functional hand grasp and arm movement to some individuals with severe spinal cord injuries.
—Recent developments in the technology of microelectrode design and neurophysiological signal analysis open the possibility of restoring greater control of motor function naturally—by thinking about moving, a technique referred to as direct brain-communication interface.

SUPPORT PLANNING GRANTS TO DEVELOP AND OPTIMIZE MODELS FOR DEPARTMENTS OF CLINICAL RESEARCH WITHIN SCHOOLS OF MEDICINE (NCRR)

—Would provide tools to develop and test models.

RESTORE THE EXTRAMURAL RESEARCH FACILITIES IMPROVEMENT PROGRAM (RFIP) FUNDS (NCRR)

—Would support construction and renovation projects at National Primate Research Centers, animal research facilities and for modem research laboratories at smaller institutions and institutions within IDeA states.

ADDRESS THE SHORTAGE OF ADVANCED INSTRUMENTATION NEEDED TO PURSUE CUTTING-EDGE BIOMEDICAL RESEARCH (NCRR)

—The High End Instrumentation program is the only NIH program that provides support for research equipment that costs at least $750,000; awards may be up to $2 million.

INTEGRATE TECHNOLOGY DEVELOPED THROUGH THE BIOMEDICAL INFORMATICS RESEARCH NETWORK (BIRN) INTO CLINICAL RESEARCH AND OTHER NEW DOMAINS OUTSIDE OF NEUROSCIENCE (NCRR)

—Some BIRN bioinformatics tools would be distributed and other tools developed; hands-on workshops to inform investigators how to use the tools for their research.
—Information technologies would be critical for scientific discovery.

NCMHD COULD STRENGTHEN AND EXPAND ITS PROGRAMS (NCMHD)

—Loan Repayment Program
—Centers of Excellence Program
—Research Endowment Program

NCMHD COULD FULLY LAUNCH ITS COMMUNITY-BASED RESEARCH PROGRAM (NCMHD)

—Would fulfill this Congressional requirement.

TRAUMA AND INJURY (FIC)

—Would initiate a new program to support research training to address the growing global burden of morbidity and mortality due to trauma and injury related to road traffic accidents, suicide and drowning, mental health consequences of

war and civil disorders, lack of emergency care and blood products and other related conditions.
—Training supported by the new program would lead to prevention strategies and interventions in wound healing, development of synthetic blood products, development of low-cost imaging technologies, mental health strategies, and epidemiology to assess risk factors as well as other activities to reduce the impact of trauma and injury to individuals, families and communities.
—Would support the establishment of a global network of highly meritorious research training centers to mitigate the impact of trauma and injury.

BRAIN DISORDERS IN THE DEVELOPING WORLD: RESEARCH ACROSS THE LIFESPAN (FIC)

—This program was begun through short term planning grants in fiscal year 2003 with the intention to grow to full research project grants in fiscal year 2005.
—The program supports collaborative research and capacity building projects on brain disorders throughout life relevant to low- and middle-income nations. Brain disorders represent a fast growing proportion of the global burden of disease.

DEVELOP THE NEXT GENERATION OF INTERNATIONAL RESEACHERS (FIC)

—It is imperative that the U.S. scientific community be prepared to tackle new threats while at the same time be positioned to work in partnership with colleagues around the world on shared problems.
—Would increase support to train U.S. medical students, graduate students and post-doctoral students in methodologies needed to tackle global health challenges.
—Would extend and intensify efforts in resource-limited nations to provide clinically appropriate, cost-effective, and sustainable care of direct health and economic benefits for the global community and mitigate the threat of disease crossing borders to affect the U.S. population.

COULD SIGNIFICANTLY EXPAND CAPABILITY TO ANALYZE, ANNOTATE, AND CLASSIFY MASSIVE AMOUNTS OF RAW SEQUENCE AND PROTEIN DATA TO MAKE IT READILY USABLE BY RESEARCHERS (NLM)

—Molecular biology is generating an unprecedented amount of genomic data that have the potential to overwhelm researchers by sheer volume.
—The protein classification project provides a valuable method to deduce the function of newly discovered proteins, greatly accelerating research in the molecular basis of disease and therapy.
—The unique and comprehensive Reference Sequence Collection would assist in studying the function of single genes and performing large-scale comparative analyses of genes across multiple organisms.

COULD ACCELERATE PROGRESS TOWARD DEVELOPMENT AND IMPLEMENTATION OF CLINICAL VOCABULARY STANDARDS THAT ARE CRITICAL TO RE-ENGINEERING THE CLINICAL RESEARCH ENTERPRISE (NLM)

—The inability to share clinical data across systems impedes clinical research and is responsible for a significant number of medical errors.
—An interlocking set of clinical vocabulary standards must be developed that incorporate robust mappings between multiple vocabularies used in clinical research and health care.
—Research, testing, and demonstration projects would help to determine best practices for incorporating vocabulary standards into clinical research, health care, and public health.

COULD WORK WITH OTHERS TO DEVELOP COMMON SOFTWARE PLATFORMS FOR ADVANCED CLINICAL AND EDUCATIONAL APPLICATIONS OF THE VISIBLE HUMAN AND OTHER IMAGE DATA SETS (NLM)

—Investments in building a Visible Human Functional Atlas of the Head and Neck and associated public software tools establish a strong foundation for developing applications software, including simulation and modeling, useful in medical training and treatment.
—Further research and testing would fully integrate the data, software, and other technology in the teaching of embryology and anatomy courses.

DEVELOP AND SUPPORT WOMEN'S HEALTH INTERDISCIPLINARY RESEARCH CENTERS ESPECIALLY IN THE AREAS OF: (OD—OFFICE OF RESEARCH ON WOMEN'S HEALTH)

—Pharmacogenetic research that focuses on sex differences in drug metabolism and biological pathways involved in the treatment of diseases such as cancer, cardiovascular disease to provide the much needed information to improve clinical outcomes, including a better understanding of the impact of pregnancy or depression on pharmacokinetics, pharmacodynamics, drug efficacy and adverse effects of therapeutic agents.

DEVELOP AND SUPPORT A CLINICAL TRIAL TO TEST A PROMISING INNOVATIVE TECHNIQUE THAT COULD REDUCE THE SIZE OF UTERINE FIBROIDS (OD—OFFICE OF RESEARCH ON WOMEN'S HEALTH)

—Could result in less morbidity for the women who face potential surgery or infertility as a result of this condition.

LAUNCH A TRANS-NIH INITIATIVE TO LEARN WHETHER eHEALTH TECHNOLOGIES ARE EFFECTIVE IN ENHANCING HEALTH BEHAVIOR CHANGE AND CHRONIC DISEASE MANAGEMENT (OD—OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH)

—Consumers, patients and providers are increasingly using eHealth applications for making health care decisions, and for obtaining and dispensing services.
—These technologies offer a potentially low cost health delivery system for underserved populations, as well as a means of supporting provider adherence to evidence-based care.

Senator SPECTER. I want to finish this question before my red light goes on to stay within the time limits. What is the status and availability and adequacy of stem cell lines for adequate stem cell research?

STEM CELL RESEARCH

Dr. ZERHOUNI. We have 17 cell lines now available. As you know, we have worked aggressively in providing infrastructure funding to all the sources that we knew were eligible for Federal funding. NIH has done every effort to expand the availability of lines. We have spent intramurally dollars to create a characterization lab. We have gone from one laboratory 2 years ago to nine laboratories doing research. So we are also realizing that training of scientists in these very difficult methods is very important. So we are doing everything we can to advance the field. So 17 lines are available to date, Senator.

Senator SPECTER. Well, I am going to violate the red light for just one question. That is not enough, is it? Those are not enough, are they? It is a leading question.

Are they?

Dr. ZERHOUNI. Well, we have a Stem Cell Task Force and Dr. Battey really works very hard with the entire community to look at what is the impact of what we need to do today of the number of cell lines. The reports that we have is that we are learning tremendously at a very high pace what are the advantages and limitations. We are looking, for example, at these issues of genetic stability and genetic diversity.

The Stem Cell Task Force at this point feels that we can do a lot of research with what we have. Can we do all of the research that will need to be done over the entire future of stem cell research? No one can say that that would be the case.

Senator SPECTER. Well, I will pursue that with Dr. Battey. I do not consider that an adequate answer, Dr. Zerhouni. It is not often

where I say your answer is not adequate, but I do not believe that is an adequate answer.

We have been joined by the distinguished ranking member, and I will yield to him at this time for 5 minutes for an opening statement or questions or however he chooses to use his time.

Senator HARKIN. Mr. Chairman, thank you very much.

Senator SPECTER. We will have second rounds, but we have Senator Stevens and Senator Cochran who are here.

STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. Well, thank you very much, Mr. Chairman. I apologize for being late. Some mornings you have to leave about 5:00 in the morning to get here because of the traffic.

It has been a privilege, Mr. Chairman, to work with you over the last 14, almost 15 years, on behalf of supporting, as you have said so many times, the crown jewel of our Federal Government, which is the National Institutes of Health. I want to thank you again for that working relationship, and I want to thank you for your great leadership, Mr. Chairman, in doubling the funding for NIH over that short period of time. It was a pleasure to work with you to do that and to continue to work with you on these crucial issues that impact the health and welfare of all of our people.

Now, unfortunately, the budget we have submitted this year is a far cry from the doubling years. I am concerned what it means for the future health of NIH. We did not double the funding for NIH to then fall off a cliff. But that is a real possibility if we continue on with this kind of budget that we have.

I want to welcome Dr. Zerhouni and the dozens of other NIH leaders who have joined us. I do not always get the time to hear from each of you, but I appreciate your being here and all the work that you do.

All of you were involved in developing the NIH Roadmap. I want to commend you for that effort. The initiative should help break down the walls between the institutes and unite everybody at NIH behind common goals. And, Dr. Zerhouni, I thank you for your leadership in encouraging that and also for your leadership in encouraging more risk-taking in the kind of applications that NIH funds. We always have to be open to new ideas. To the extent that I can, I hope to back you up. People may say, well, why are you funding some of these far-out things? Well, because sometimes we want to take a look at them. And I really applaud you for doing that.

I just got here to hear a little bit about the stem cell issue. We have discussed that many times before here. We know that this research offers enormous potential to help ease the suffering of people with Parkinson's and juvenile diabetes, ALS, Alzheimer's.

I just had the occasion last evening to meet an old friend of mine who I had not seen in several years. I found out that he has Lou Gehrig's disease. It was just a startling thing for me to see that last evening. His words to me were, you have got to put more research into the stem cell research and find out what is going on here. To see someone that you have known for a long time and then you lost contact with him and then you see him and you know

they are not going to be around very much longer and they are in middle stages of Lou Gehrig's disease, it is a tough thing to see.

I am just concerned that the restrictive policies in this research are delaying the day when these diseases could be cured. Under the President's guidelines only those cell lines generated before the arbitrary date of August 9, 2001 at 9 p.m.—not 9:30, not 8:45, but at 9 p.m., very arbitrary—can be approved for federally approved research. The President said then there were more than 60 eligible lines. Later we heard there were 78. Now I just think I heard from you there were 17 that are available to researchers. Well, I will ask some questions about this during my period of time.

These 17 were also grown on mouse feeder cells, all of them, which raises questions whether or not they can ever be used for any kind of human therapies.

Meanwhile, scientists in other countries are moving ahead, but we cannot fund those. We cannot fund any of that kind of research because those lines were developed after August 9, 2001 at 9 p.m. So again, I will get into that in my question and answer period.

I thank you for letting me make my opening statement, and whenever I can get a chance to ask questions, I will——

Senator SPECTER. Thank you, Senator Harkin. We will come back to another round.

Senator Stevens.

Senator STEVENS. Thank you very much.

Dr. Zerhouni, it is nice to see you here. I do not think we have ever had an opportunity to put visuals on all of these people that you have brought here with you today. So I want to thank you for coming and apologize to them for taking their time. I do not know of another group that is more important to the future of our country than maybe now the intelligence community might be that would have a similar impact in the long range, but this long-range impact of you and your colleagues is just staggering.

I heard the comments of my friend, Senator Harkin. Senator Connie Mack came to me and urged me to support a concept of doubling the NIH budget, and we have done that, Senator. So the real question I think we have to do one of these days is analyze what have we achieved with that money. I do think that that is something that you and your assembled colleagues could help us on. We are currently looking to increase other areas now, the National Science Foundation for one and the intelligence community for another. So the doubling of those budgets in the next 5 years will take precedence I think because of the circumstances that exist in the country.

PROSTATE CANCER

I am glad to see Dr. von Eschenbach here. My good friend, Mike Phelps, reported you gave a tremendous speech at the molecular imaging meeting in Orlando. Several of you know my continuing interest in PET and its application to various areas of your institutes. I do hope that we can be able to be very aggressive in the use of that, the total molecular imaging concepts, to Alzheimer's, which I believe is becoming a great problem as the baby boom generation reaches retirement age.

But I have one specific question. Prostate cancer is also a personal interest. I am a survivor now for 12 years. I would be interested if Dr. von Eschenbach would comment upon finasteride and what's going to happen to that clinical trial. I understand the clinical trial was canceled and there were some problems. Was the FDA a problem or was it that the high rate of tumor growth in those taking the drug? What happened, Doctor?

Dr. VON ESCHENBACH. Well, thank you, Senator, for that important question because I think it really underscores and points out not only the tremendous progress that we are making, but also how the investment that you have been responsible for in biomedical research is really now making it possible for us to solve problems that before we did not even understand.

The issue with regard to the prevention trial of prostate cancer using finasteride demonstrated that in fact the drug did reduce the number of men who developed prostate cancer. So in that regard, we stopped the trial because the endpoint had been achieved. We in fact did get the answer and got the answer earlier than we had hoped or anticipated and demonstrated the protective effect of finasteride for a number of men who were susceptible to prostate cancer.

What we also recognized in that trial was that although fewer men developed prostate cancer on finasteride, the kind of prostate cancer that they developed appeared to be more virulent and more aggressive, and perhaps could even increase their risk of progression or dying from prostate cancer.

So in addition to demonstrating the protective effect, what we have now launched into is a subsequent set of studies to understand the mechanisms of action and to determine the impact on virulence. That is now an ongoing part of our research investigation.

Senator STEVENS. Thank you very much on that.

Mr. Chairman, I do have, unfortunately, on the schedule several other subcommittees meeting. Again, I want to thank you for bringing all of the directors of these institutes here. I urge you to let them go quickly so they can go back to work.

Senator SPECTER. That concludes the hearing.

Senator STEVENS. It concludes my time too. Thank you all very much.

Senator SPECTER. Thank you very much, Senator Stevens.

I am going to step out for a moment down the hall to the Judiciary Committee to see if I am needed for a quorum there. I hope to return within the time allotted to Senator Cochran, but if I do not, we will turn to Senator Harkin. Senator Cochran.

Senator COCHRAN. Mr. Chairman, thank you.

Dr. Zerhouni, we are very pleased with the fact that you are exploring research possibilities in areas that have previously been, I think, relegated to a fairly low priority. Fundamental challenges such as understanding obesity, its effect on health, what can be done to both treat those symptoms and, more importantly, prevent that condition should be the subject of research. I wonder what emphasis is placed in the budget request with regard to research in this area.

OBESITY RESEARCH

Dr. ZERHOUNI. This is a very important topic to us. Actually I would like to point out that NIH has been working on obesity for over 10 years. I actually have a little graph here that you could see whereby our investments started in 1996 because already at that time, NIH had predicted that the obesity crisis will hit, and it became one of the top 10 topics of research.

However, as you know, the rate of increase of obesity is actually greater than what we expected, so we are increasing our funding at the same level. In fiscal year 1996, we had $86 million. Next year we will have $440 million funding. Last year I established a trans-NIH Obesity Task Force, led by Dr. Allen Spiegel and Dr. Barbara Alving. They have come up with a new strategic research plan for obesity, and despite the difficult budget environment, we are going to increase our funding from $400 million to $440 million in obesity research by $10 million. So we have almost quadrupled our investment in obesity research while the rest of the NIH doubled to show you our commitment to it and also our ability to see proactively where research needs to be.

Senator COCHRAN. I hope you will take into account the importance of concentrating some of this funding in areas that suffer from this in a disproportionate way compared to the rest of the country.

Dr. ZERHOUNI. Actually, Senator, this is one of the priorities of the new plan. We are going to focus on childhood obesity which affects rural areas and minority areas to a much greater degree than other communities. So we will have an implementation to be able to study that pattern early on in life.

ROLE OF THE NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Senator COCHRAN. One new phenomenon I know is the fact that millions of Americans are using dietary supplements and herbal products today. The National Center for Complementary and Alternative Medicine is playing a role in understanding the efficacy and the effects of these products. What are your plans for research with respect to these products?

Dr. ZERHOUNI. If you allow me, I would like Dr. Stephen Straus, who is the Director of the National Center for Complementary and Alternative Medicine, to answer that. He has very definite plans and great strategies for that.

Dr. STRAUS. Thank you. Mr. Cochran, our goal is to characterize the complementary and alternative medicine (CAM) products that Americans are using, understand why they have the activities they do, and then prove whether they are safe and effective. We are doing this in a multi-tiered approach, much of which is conducted in partnership with the other NIH Institutes and Centers because of their strong areas of thematic expertise.

We are doing this with products that are used for neurodegeneration such as ginko biloba. In that regard, we have already enrolled, in partnership with the National Institute of Aging, the National Heart, Lung and Blood Institute and the National Institute of Neurological Disorders and Stroke, over 3,000 patients in

the largest study ever mounted of an herbal product, and at that time the largest preventative study conducted for dementia. The goal is to prevent the onset of Alzheimer's disease in otherwise healthy, aging Americans.

At the same time we are studying mechanism, and in your own State, we have funded outstanding investigators at the University of Southern Mississippi who are showing us several different chemical constituents in ginko that prevent the death of neuronal cells in the brain. These are our strategies.

Senator COCHRAN. Thank you very much.

THE NATIONAL INSTITUTE FOR BIOMEDICAL IMAGING AND BIOENGINEERING

I appreciate also the NIH's recognition of the role for new technologies in the detection and treatment of disease. The National Institute for Biomedical Imaging and Bioengineering was created specifically to enhance research in this area. Has this investment begun to show results, Dr. Zerhouni?

Dr. ZERHOUNI. I think so. One of the most important meetings that the institute has had was actually organized at the University of Mississippi. It was a national strategic meeting to try to see where the direction of the field would go. Dr. Pettigrew is really a great leader and I would like him to comment, if you do not mind, Senator.

Senator COCHRAN. Thank you.

Dr. PETTIGREW. Thank you, Senator, and I appreciate having the opportunity to respond to that question.

There are many problems that physicians alone cannot solve. There are problems that also require the input of quantitative scientists. These would be scientists, which include not only imagers and physicists but also mathematicians and computer scientists.

We have been very successful, I am pleased to report, in bringing physicians and quantitative scientists together to translate the fundamental discoveries from the technologically-based scientists into meaningful clinical applications for patients. That is certainly our goal and we work very hard to achieve that.

The progress to date has been quite remarkable given our short history of only 2 years. I would like to tell you about two examples in this area.

NIBIB'S PROGRESS

The first is the development of a new technology called quantum dots. These are small nano crystals that are able to identify specific cells of interest in the body, for example, cancer cells in lymphnodes. Quantum dots could also be used to identify the deposition of plaque in arteries.

We have also seen progress in an area that many people in the audience might appreciate. No doubt people here have had MRI scans. This is a marvelous technology, in fact, the subject of the Nobel Prize in Medicine this year. But some of our researchers have tackled one of the problems, which is the speed with which these scans can be made. These researchers have improved the speed of acquisition of images 10-fold. Studies that used to take several minutes to acquire can now be acquired in a matter of sec-

onds. The value of this is not only in improved patient comfort, but also in opening up additional applications such as image-guided surgery where speed would be very important.

These are examples of some of the technological innovations that we have been pursuing and have begun to bring to fruition for the benefit of us all.

Senator COCHRAN [presiding]. Thank you. Thank you very much, Mr. Chairman.

Senator Harkin, do you have questions?

Senator HARKIN. If you want to have a follow-up.

Senator COCHRAN. No. Go ahead. I am trying to carry out the chairman's 5-minute rule here. No, go ahead, please proceed.

Senator HARKIN. Okay, thanks.

STEM CELL LINES

I would like to get back to the stem cell issue, if I could, and I would like to direct some questions to Dr. Battey. I believe you are heading the Stem Cell Task Force.

Dr. BATTEY. That is correct.

Senator HARKIN. Correct me if I am wrong, but I think you have said that under the best case scenario, only 23 lines will be available to federally funded scientists. Is it 23 or is it 17? I am a little confused there.

Be that as it may, even if it is 23, my question basically is will 23 be enough to realize the full potential of stem cell research?

Dr. BATTEY. Let me begin by addressing the numbers issue that you have raised.

The number 17 refers to the number of cell lines that are available today for Federal funding that can be widely disseminated across the research community, cells that—if you had a laboratory—you could order and get in your laboratory for experiments. There are six additional derivations located at institutions that hold NIH infrastructure awards for the purpose of developing such cell lines, expanding them, getting them ready to be distributed, going from a derivation to a useful cell line that can be distributed. And we are hopeful that all six of these will become distribution quality cell lines. When you add 17 and 6, one arrives at the figure 23.

Now, there are 31 derivations located in five institutions in Korea, India, and Sweden that are eligible for Federal funding that are on the registry, but they have not sought an NIH infrastructure award to develop such cell lines. So we do not know the status of these derivations. They are privately held and we are not privy to that information.

Senator HARKIN. Let me get to my question there, Dr. Battey. Will 23 or 17 be enough to realize the full potential of stem cell research?

Dr. BATTEY. I do not know the answer to that question, but there are reasons to be concerned. For example, there was a published paper in December showing that when some of the cell lines, some of the 17, are grown in some people's hands and passaged for prolong periods of time, they develop karyotypic abnormalities, chromosomal abnormalities. These abnormalities are some of the same abnormalities that are seen on occasion in teratocarcinomas, which

are tumors of cells like embryonic stem cells. That is an issue of great concern and will need to be followed very carefully.

While I have to say I do not know whether or not we will be able to do everything possible with either 17 or 23 or 46 or 98 or 321 cell lines, I do know that if there is additional functional diversity it is difficult to imagine that more cell lines would be detrimental to research progress.

MOUSE FEEDER CELL LINES

Senator HARKIN. Could any of these 23 lines ever be used in human therapy since they have all been developed on mouse feeder cells?

Dr. BATTEY. We have discussed this issue at great length with the Food and Drug Administration, who would be the organization overseeing the safety and efficacy of any clinical studies that were done with these cells, were these cells to ever be returned to patients in transplantation in an effort to treat some of these awful disorders like ALS that you have spoken about. When we talk to the FDA about this, they say that the mouse feeder cell layer is an issue and the issue of whether or not a retrovirus or some other bad thing might have been transferred from the feeder cell layer to the human embryonic stem cells is an issue that must be explored.

It is not, however, a prohibitive issue. It is one of many issues, including the history of the cells, where they have been cultured, what kind of medium they have been cultured in, if there have been any serum or other biological additives, what the state and purity of those are. So there is no question the feeder cell layer is a safety issue, but it is one of many safety issues and I do not think should necessarily be drawn out of that context.

Would it be preferable to have cells that were not growing on mouse feeder cell layers? I think the answer to that question is yes. Would it be preferable to have cells that were grown in a medium that had nothing but completely defined substances, purified additives? Absolutely. That would be better. In fact, the NIH is funding investigators to try to develop better culture conditions for human embryonic stem cells with the goal of ultimately moving the cell lines into an environment that poses less questions about biological safety.

ACCESS TO ADDITIONAL LINES

Senator HARKIN. The other question I had was basically would federally funded scientists benefit from having access to additional lines. I think you basically answered that. Obviously, the more you have and the more involved, I would assume the better the research would be. You would have just more lines out there to look at.

Dr. BATTEY. We will understand much better what the significance of number of cell lines is when we have explored to a greater degree what we can do with the cells that are available and widely distributed for Federal funding. But as I said before, it is difficult to argue that a greater number with more potential functional diversity would be detrimental to the research effort.

Senator HARKIN. If they had access to additional lines—lead me on. I just want to get a better understanding. How would this be not detrimental if they had more?

Dr. BATTEY. Well, the problem here and the reason why I cannot be more specific in answering this question is that we are just at the beginning of exploring what we can do with the cell lines that are eligible for Federal funding. We are just beginning to learn the master switches that keep these cells in a pluripotent state and allow them to replicate indefinitely in the laboratory. We are just beginning to get our hands around the growth factors and gene expression profiles that are associated with differentiation towards a cell type that might be interesting for a therapeutic application such as a dopamine-producing neuron that might be lost in a patient with Parkinson's disease or a motor neuron that will be lost by your friend with ALS. We are only beginning to understand, and until we know more about what we can do with the cells we have, what their limitations are, what their possibilities are, it is hard for me as a scientist in a fact-based manner to give you a better answer than the one I have given, as much as I would like to do that.

STEM CELL POLICY

Senator HARKIN. Is it time to reevaluate the policy that has been in effect since August 2001?

Dr. BATTEY. I think it is very important for there to be a continued dialogue between scientists, the National Institutes of Health, your subcommittee, and the administration about what the state of the science is. The decision to evaluate a presidential policy is a decision that is made at the level of the White House. Our role in this process, as I understand it, is to provide facts and information for the people who make policy, and we have a regular dialogue with individuals in the administration, as well as individuals on some of your staff about the state of the science in human embryonic stem cells. Just on a personal note, I am happy to come and talk to anybody who has questions or wants to know more about the state of the science in what I consider to be one of the most exciting areas of science for the future of biomedical research.

Senator HARKIN. Thank you very much, Dr. Battey.

Senator SPECTER [presiding]. Thank you, Senator Harkin.

Dr. Battey, the Congress also has a constitutional role in setting national policy and that starts with this subcommittee. Dr. Zerhouni and Dr. Battey, as the area of responsibility may fall, we would like to have a comprehensive report on what has happened to the original 60-some stem cell lines announced by the President back in August of 2001 and what has happened to them, how many are in private hands, how many of them are tainted with mouse feeders, how many of them can be used, what is happening at Harvard, what is happening in South Korea, what is happening in other countries so we can make an evaluation as to what the policy ought to be.

[The information follows:]

STEM CELL RESEARCH

Question. What is the status of human embryonic stem cell (hESC) derivations listed on the NIH Stem Cell Registry? How many are in private hands? How many have been grown on mouse feeder layers? How many are viable?

Answer. All of the derivations listed on the NIH Human Embryonic Stem Cell Registry are privately owned by 15 different companies or academic institutions. The providers indicated by an asterisk (*) below are recipients of the NIH Infrastructure award to develop, characterize and distribute cell lines.

*BresaGen, Inc., Athens, Georgia**

4 derivations
3 lines available
The cells in derivation BG04/hESBGN–04 failed to expand into undifferentiated cell cultures.

Cell & Gene Therapy Research Institute (Pochon CHA University), Seoul Korea

2 derivations
0 lines available

*Cellartis (formerly Cell Therapeutics Scandinavia), Göteborg, Sweden**

3 derivations
2 lines available
Cell line SA03/Salgrenska 3 was withdrawn by donor.

*CyThera, Inc., San Diego, California**

9 derivations
0 lines available
The cells failed to expand into undifferentiated cell cultures.

*ES Cell International, Melbourne, Australia**

6 derivations
6 lines available

Geron Corporation, Menlo Park, California

7 derivations, all duplicates of Wisconsin Alumni Research Fdn. derivations

*Göteborg University, Göteborg, Sweden**

16 derivations, reported to have not been exposed to mouse feeder layers
0 lines available

*Karolinska Institute, Stockholm, Sweden**

6 derivations
0 lines available
The cells failed to expand into undifferentiated cell cultures.

Maria Biotech Co. Ltd.—Maria Infertility Hospital Medical Institute, Seoul, Korea

3 derivations
0 lines available

*MizMedi Hospital—Seoul National University, Seoul, Korea**

1 derivation
1 line available

National Centre for Biological Science/Tata Institute of Fundamental Research, Bangalore, India

3 derivations
0 lines available

Reliance Life Sciences, Mumbai, India

7 derivations
0 lines available

*Technion-Israel Institute of Technology, Haifa, Israel**

4 derivations
2 lines available

*University of California, San Francisco, California**

2 derivations
2 lines available

*Wisconsin Alumni Research Foundation, Madison, Wisconsin**

5 derivations
5 lines available

Of the 78 entries on the Registry, 71 are from independent embryos and 7 are duplicates located at both WiCell (Wisconsin Alumni Research Fdn.) and Geron. The Geron cell lines are not being widely distributed to the research community.

Of the 71 independent derivations:

—16 have failed to expand into self renewing, pluripotent cell lines (9 at CyThera, 1 at BresaGen, 6 at Karolinska), and 1 line was withdrawn by the donor at Cellartis (formerly Cell Therapeutics Scandinavia, CTS). NIH provided Infrastructure support in failed attempts to expand these 16 derivations into distribution-quality cell lines.

—Of the remaining 54 independent derivations, 21 are available for shipment, after expansion and characterization using NIH Infrastructure grant awards. The 21 that are currently available are:

BresaGen, Inc.—BG01, BG02, BG03
Cellartis—SA01, SA02
ES Cell International—ES01, ES02, ES03, ES04, ES05, ES06
MizMedi Hospital—MI01
Technion-Israel—TE03, TE06
UCSF—UC01, UC06
WiCell—WA01, WA07, WA09, WA13, WA14

—Of the remaining 33 independent derivations, 2 more are at institutions with NIH Infrastructure awards. If these 2 were developed into distribution quality cell lines ready for shipment, there would be 23 independent cell lines available to the research community. The 2 cell lines under development are:

Technion-Israel—TE04, TE07

—The remaining 31 independent derivations are all at institutions located outside of the United States that have not applied for NIH Infrastructure awards to develop their cell lines. Any plans to develop these derivations into cell lines that are available to the research community are unclear at this time. The 31 derivations at institutions that do not have Infrastructure awards are:

Pochon CHA (Korea)—2 derivations
Göteborg Univ. (Sweden)—16 derivations
Maria Biotech (Korea)—3 derivations
National Centre for Biological Sciences (India)—3 derivations
Reliance Life Sciences (India)—7 derivations

As far as we know, all derivations have been exposed to mouse feeder cells, with the exception of the 16 derivations at Göteborg University (Sweden).

Information on the detailed characteristics of each of the derivations is available on the NIH Human Embryonic Stem Cell Registry, http://escr.nih.gov.

Question. What is Happening at Harvard University?

Answer. On March 25, 2004, Harvard University announced the derivation of 17 hESC lines in an article published in the New England Journal of Medicine. Funding for the derivations and distribution of these lines is being provided by the Howard Hughes Medical Institute, Juvenile Diabetes Research Foundation and Harvard University.

On April 23, Harvard University announced the establishment of the Harvard Stem Cell Institute. According to Harvard, the Institute will encourage adult and embryonic stem cell research using both animal and human stem cells. The Institute has two co-directors: Harvard Medical School Professor David Scadden, who also directs Massachusetts General Hospital's Center for Regenerative Medicine and Technology, and Douglas Melton, the Thomas Dudley Cabot Professor of the Natural Sciences and a Howard Hughes Medical Institute investigator.

Research at the Institute will be focused on five areas of disease for which stem cell therapy seems most promising. The diseases all result from some sort of organ or tissue failure and include: diabetes, neurodegenerative diseases, blood diseases, immune diseases, cardiovascular disease, and musculoskeletal diseases.

Although research on the 17 new human embryonic stem cell (hESC) derivations are not eligible for Federal funding, NIH is currently supporting several scientists at Harvard University whose hESC research use lines eligible for Federal funding. Dr. Doug Melton is working to identify the genes involved in hESC self-renewal and differentiation. Dr. George Daley is studying hematopoietic development from hESCs. Dr. Howard Green is working to develop the culture conditions to coax

hESCs to become the keratinocytes that make up human skin(s epidermis. Dr. Jeffrey Harper is analyzing the signals that control hESC division.

Question. What is Happening in South Korea? What is Happening in Other Countries?

Answer. On February 12, 2004, South Korean researchers published the first scientifically credible report of the creation of a cloned human embryo in the laboratory by means of somatic cell nuclear transfer (SCNT) (Science 303: 1669–1674.) These scientists, supported by the South Korean government, then used these cloned embryos to establish a human embryonic stem cell line. They combined the DNA of a woman's ovary cell with her donated egg, from which the nucleus had been removed, and then stimulated the newly combined cell to divide. The resulting very early embryo was then allowed to develop to the blastocyst stage (five to nine days), at which point it was disaggregated and the highly potent stem cells of the inner cell mass were removed. These stem cells were then treated to produce a stem cell line to be used for various kinds of biomedical research. Subsequent to the publication of the SCNT study, the South Korean government voted to ban the creation of cloned human embryos, but might allow cloning for biomedical research on a case-by-case for medical treatment subject to approval by a National Bioethics Advisory Commission. Scientists will be permitted to use spare frozen embryos, left over from infertility treatments and kept in laboratories for at least five years, for limited stem cell research into treatments for hard-to-cure diseases. The regulations banning human cloning are expected to come into effect after President Roh Moohyun signs the bill. The regulations on stem cell research will go into effect in 2005.

OTHER INTERNATIONAL STEM CELL EFFORTS

International Society for Stem Cell Research (ISSCR).—The International Society for Stem Cell Research is an independent, nonprofit organization established to promote and foster the exchange and dissemination of information and ideas relating to stem cells, to encourage the general field of research involving stem cells and to promote professional and public education in all areas of stem cell research and application. Opinions on the legitimacy of experiments using human embryos vary among members of the European Union (EU) according to the different ethical, philosophical and religious principles in which they are grounded. EU member states have taken very different positions on the regulation of human embryonic stem cell research and cloning for biomedical research. More information about the regulations and policies of EU members can be found on the website of the ISSCR at the following link: http://www.isscr.org/scientists/legislative.htm.

The International Stem Cell Forum (ISCF).—The ISCF was founded in January 2003 to encourage international collaboration and funding support for stem cell research, with the overall aim of promoting global good practice and accelerating progress in this vitally important area of biomedical science. The Forum's long-term aim is to help stem cell scientists achieve a range of revolutionary medical advances that will benefit people throughout the world. The ISCF is led by the United Kingdom's Medical Research Council and consists of 14 leading supporters of stem cell research from around the world. Member organizations are based in the United States, Finland, Australia, Canada, Germany, France, Israel, Netherlands, Japan, Singapore, Sweden, Switzerland, and the United Kingdom. Within ISCF, the United States is represented by the NIH. The Juvenile Diabetes Research Foundation International (JDRF) is also a member of the ISCF. One short term goal of the ISCF is to compare different stem cell lines from the member organizations. As part of this goal, NIH's federally approved stem cell lines will be compared to those of other member organizations. Information about the stem cell research efforts of the member organizations can be found on the website: http://mrc.live.tmg.co.uk/.

Senator SPECTER I have discussed it with the President and he has a view on it. The facts are very important in formulating all of our views. So let us proceed to bring all the facts to this subcommittee.

Dr. ZERHOUNI. You have my commitment to do so, Senator.

BIODEFENSE AGENTS

Senator SPECTER. Thank you very much.

On the issue of biodefense, the concerns about another attack are with us imminently as we sit here. We have seen an acceleration of the venom and hatred from Wahabes and Islam fundamentalism

and we have a long chronology of attacks going back to 1983 when 283 Marines were killed in Lebanon, what happened in Mogadishu, what happened in Africa in August 1998, what happened with the Cole, what happened on 9/11. We have to be prepared.

Dr. Fauci, you and I have discussed this on other occasions. This year's request includes $1.7 billion toward biodefense research activities. What are the principal bioweapons that we are working to defend against?

Dr. FAUCI. The principal bioterror agents that we are involved in pursuing from the standpoint of developing countermeasures remain the category A agents that we have discussed before this committee on several occasions. High among those are still smallpox, anthrax, botulism toxin, tularemia plague, and the hemorrhagic fevers including Ebola. We are pleased to report, as Dr. Zerhouni mentioned in his opening statement, that over the past year with the resources that this committee has generously given us, we have made extraordinary progress in having available, either already in the stockpile or in contract on its way either in phase I/II or purchase, countermeasures in the form of vaccines for smallpox, anthrax, and soon Ebola.

Senator SPECTER. If there was to be an attack on anthrax, how well prepared are we?

Dr. FAUCI. We are extraordinarily better prepared today than we were in the anthrax attacks in the fall of 2001 with the following issues. A, the stockpile of antibiotics right now to treat prophylactically for the entire 60-day period with ciprofloxacin or doxycycline is now able to meet a substantial attack, God forbid that were to occur. And also, we are now well into the development of the second generation of a recombinant protective antigen anthrax vaccine that could be used to vaccinate people who would go in to clean up, the hazmat people, health workers, and those who would be required to have an extended period of antibiotics. So the anthrax situation is dramatically different than it was in this building a year and a half, 2 years ago.

Senator SPECTER. Adequate?

Dr. FAUCI. I believe adequate. I think we still have a ways to go on every issue, but the progress that is being made particularly in the arena of anthrax is striking.

Senator SPECTER. My red light is about to go on. So I would like you to supplement in writing the details as to the other threats, what we have done, whether it is adequate, and what more needs to be done.

Dr. FAUCI. I would be happy to do that.

Senator SPECTER. This is something we have to address forcefully and promptly.

Dr. FAUCI. Will do.

[The information follows:]

RESEARCH IN MEDICAL COUNTERMEASURES AGAINST CATEGORY A BIOLOGICAL AGENTS

The accompanying table provides a summary on the status of research and development of medical countermeasures for Category A biological agents. These biological agents and the countermeasures that are currently available for them are identified in the first two columns. Recent NIAID accomplishments are identified in column three (complete details of these and additional accomplishments can be found

in the *NIAID Biodefense Research Agenda for CDC Category A Agents Progress Report)*.[1] Candidate countermeasures that are at an advanced research stage where rapid development of the countermeasures is scientifically feasible are identified in the fourth column. Finally, many of the countermeasures that are the focus of early research efforts are identified in the last column.

I would like to add that we continue to support a national, comprehensive biodefense research and development program. It includes the development of other biodefense countermeasures to combat Categories B and C biological agents, as well as a broad range of basic research activities.

[1] See http://www2.niaid.nih.gov/Newsroom/Releases/biodefensereport2003.htm for a detailed report on research progress made to date for CDC Category A Agents.

STATUS OF NIAID RESEARCH IN MEDICAL COUNTERMEASURES AGAINST CATEGORY A BIOLOGICAL AGENTS

Organism	Countermeasures Currently Available	Recent NIAID Accomplishments	Current Product Development Efforts	Focus of Early Research Efforts
Bacillus anthracis (Anthrax)	• Several antibiotics, useful if begun very early after infection • Limited quantities of Anthrax Vaccine Absorbed (AVA) available from DoD and CDC for use under IND • Supportive care	• Initiated advanced development of anthrax rPA vaccine • Completed computer model examining the optimum duration of antibiotic prophylaxis after anthrax exposure • Continued the evaluation of antibiotics currently licensed for other infections	• Recombinant Protective Antigen (rPA) vaccine • Antibiotics licensed for other infections	• Alternate/next generation vaccines • New/better antitoxins and antimicrobials • Basic pathogenesis studies to better understand potential targets for genetically engineered resistance
Clostridium botulinum (Botulism)	• Very limited quantities of polyclonal antibodies available from DHS and CDC for use under IND • Supportive care	• Discovered a cocktail of 3 monoclonal antibodies that potently neutralize botulinum neurotoxin types A1 and A2 in small animal models	• Monoclonal Antibodies • Recombinant botulinum vaccine active against 3 serotypes	• Alternate/next generation vaccines (recombinant toxin fragment) • New/better antitoxins; small molecule inhbitors and other novel synthetic molecules • Exploring toxin stability in the environment
Yersinia pestis (Plague)	• Several antibiotics, useful if begun very early after infection • Supportive care	• Developed mouse model of plague to be used for evaluating new vaccines • Continued the evaluation of antibiotics currently licensed for other infections	• Protein subunit vaccines (FY04 NIAID initiative) • Antibiotics licensed for other infections	• Basic pathogenesis studies to better understand potential targets for genetically engineered resistance • 2nd generation vaccines • New/better antimicrobials
Variola virus (Smallpox)	• Wyeth (Dryvax) vaccine • Aventis Pasteur vaccine • Acambis cell cultured vaccine • Cidofovir for treatment of smallpox and vaccine side effects for use under IND • VIG for vaccine side effects • Supportive care	• Initiated development of MVA vaccine • Screened >950 compounds *in vitro* for activity against poxviruses; tested ≈40 active drugs in animals • Developed IND for cidofovir as primary treatment for smallpox or complications with vaccination • Continued to develop two monkey smallpox models to evaluate drugs/vaccines (with USAMRIID and CDC)	• Advanced development of MVA vaccine – safer alternative; could be used in immunocompromised population (3rd generation) (FY04 NIAID initiative) • Licensed antivirals and antivirals against other viral infections currently under development by industry • Development of oral derivative of Cidofovir	• Easily administered, antiviral drugs • Safer vaccines • Monoclonal antibodies to replace VIG
Francisella tularensis (Tularemia)	• Several antibiotics, useful if begun very early after infection • Supportive care	• Initiated collaboration with DoD to further develop candidate tularemia vaccine (live vaccine strain - LVS)	• Live attenuated and sub-unit vaccine candidates (FY04/05 NIAID initiatives)	• Antimicrobials and immune-based therapies with novel mechanisms of action • Antibiotics licensed for other infections
Viral Hemorrhagic Fevers (note this includes several families of viruses)	• Limited quantities of partially effective, unlicensed vaccines for Junin and Rift Valley Fever viruses available from DoD for use under INDs • Ribavirin effective in the treatment of some viral infections (e.g. Hantavirus and Lassa) • Supportive care	• Demonstrated that fast-acting vaccine protects monkeys from Ebola (with USAMRIID) • Initiated first human trial of DNA-based vaccine for Ebola • Methods developed to study individual proteins from these viruses in regular, low containment laboratories.	• Ebola vaccine • Rift Valley Fever vaccine (preclinical studies) • Marburg vaccine (preclinical) • Lassa vaccine (preclinical) • Dengue vaccine (preclinical)	• Broad spectrum antiviral drugs • Immune-based therapies • Vaccines against the major threat agents • Combination vaccines which are broadly protective

Senator SPECTER. Senator Harkin.

Senator HARKIN. Thank you, Mr. Chairman.

FUNDING OF RESEARCH GRANTS

Dr. Zerhouni, our staff has brought to our attention this issue of the number of research grants that we are funding this year. It is a question we always ask. What are we doing in terms of the number of grants and the funding for these grants?

I have found—and you correct me if I am wrong on this—that fiscal year 2004 marked the first time in 8 years that the number of new competing grants went down. It dropped from 10,393 in fiscal year 2003 to 10,135 in fiscal year 2004. That is the bad news. We might say, well, but the good news is the President's 2005 budget calls for raising that number back to the 2003 level of 10,393. So I said, okay. How do we do that?

As you know, when researchers get approved for NIH grants, for the second, third, fourth years, there is an automatic 3 percent increase. Well, what I found out is that this longstanding commitment by NIH to these researchers is necessary so that they can pay their staff and give them their annual salary increases or get new equipment and so forth in the second, third, and fourth years. Now, that is 3 percent. And this year's budget calls for an increase of 1.9 percent to the second, third, and fourth year researchers. As a result, the researchers will receive less money than what NIH committed to providing them.

I am wondering about the effect this is going to have. Could it force them to change the scope of their work in midstream?

Now, again, I think that you and all of us are opposed to breaking NIH's commitment to its grantees. Once you make a commitment, you make a commitment. And I am concerned that this budget is changing this policy, and I am wondering why are we changing this policy. Why are we going to 1.9 percent rather than 3 percent?

Dr. ZERHOUNI. These are very important questions and those are the questions we have grappled with in a very difficult budget environment and we had to make tough choices.

But let me address your first question which was that a decrease between 2003 and 2004 and then recovery in 2005 in numbers of grants. Fiscal year 2003 was the last year of the doubling of the budget.

Senator HARKIN. Right.

Dr. ZERHOUNI. We actually gave more grants in 2003 than we planned to do so that is why the number in 2003 was higher. In 2004, we were planning on keeping that level or even go up a little bit, but certain budgetary events occurred.

One, was the .59 percent cut across the board. That was in conference.

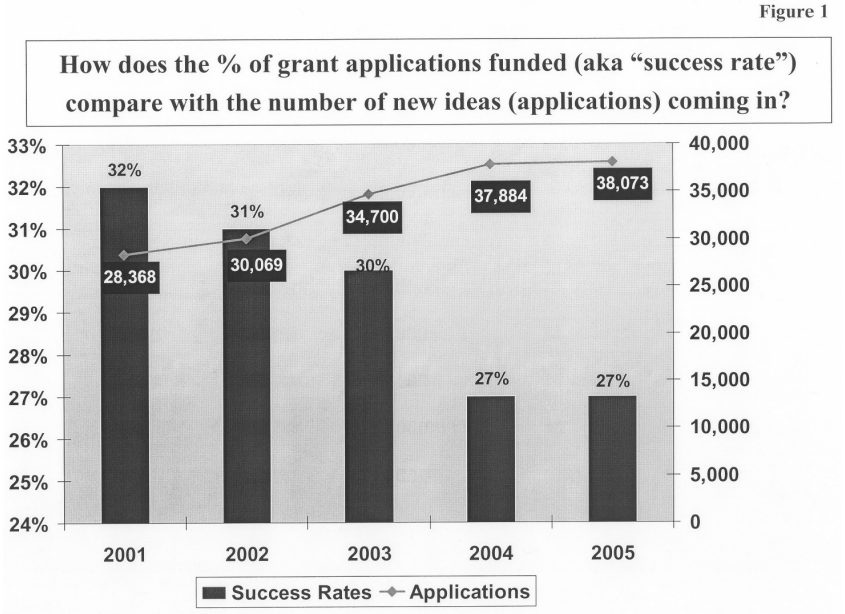
Second was the reshifting of extramural construction, $119 million we had not requested. It was then put back into the extramural construction.

Last but not least was what we call the planning and evaluation tap, 2.2 percent of the NIH budget is used to fund AHRQ, for example. So all of these elements decreased the funds available for the grant pool in 2004.

Now we come to this year and we have a budget envelope of 2.6 percent. So we had to make tough choices.

I agree with your policy principle. This is something that I have told all the Institute and center directors—that our word is our bond. We should really commit to maintaining research grants at least at an inflationary level so that they do not lose the ability to purchase research, if you will.

Figure 1



SUCCESS RATES

But on the other hand, we also have a marked increase in terms of applications and new scientists are coming to us asking for grants. So we had to make a tough decision. I have the information here to show you on the screen. If you looked at our success rate at the beginning of the doubling, our success rate was 32 percent here. The number of applications we received in 2001 was 28,000. Senator, the number of applications we are receiving is now 38,000. This year alone our Center for Scientific Review will receive 66,000 applications for all types of grants for NIH as well as some from CDC, AHRQ, FDA, and SAMHSA.

Senator HARKIN. Excuse me, Dr. Zerhouni, but that 38,000 and the 37,000 and the 34,000 I see, are those the ones that actually make it through the peer review process?

Dr. ZERHOUNI. Those are the ones that are applied for. They are new and competing in that year. Only one-third of them will get funded.

So, for example, if you go back to 2001, Senator, we had 28,000 grants. Thirty-two percent of those were funded. Then we had 30,000 applicants. Thirty-one percent of those were funded. And then in 2003, we had 34,700 applications.

So from my standpoint, as you look at the budget and you look at the number of scientists out there who are coming up with great ideas, we had to make a choice. Can we shave the cost increases to allow more of these increasing numbers of scientists to apply and be successful? So those are the tensions, Senator, that I had to deal with in making the tough decisions.

Senator HARKIN. Well, I understand the dilemma you were faced with. I guess under the budget we have got a choice, either increase the number of new grants and cut back on the increases for those that are already approved, or keep the increases in and not have new grants.

Dr. ZERHOUNI. That's right.

Senator HARKIN. That seems to be the dilemma.

Well, I do not know. Maybe we made the right decision, but I just think we all ought to be aware, Mr. Chairman, of the tradeoff that we have made with this budget. Now, I am preaching to the choir here because this person right next to me here keeps going on the floor trying to get our budget up for NIH and I have backed him every time we have tried to do that. But because of this budget, you have had to make almost a devil's choice here in terms of the tradeoff. As you say, you want to keep your word. You want to keep your commitment to these researchers. But then the President's budget—it is his budget—wants to have all these new starts, so then you have to trade that off. I think that is why we need to actually get this budget back up again so that that does not happen.

PROJECTING OUT-YEAR BUDGETS

Now, I am particularly concerned, as I said in my opening statement, about the years ahead. According to OMB, NIH's budget is expected to drop in actual dollars by 2 percent in fiscal year 2006. If that goes through, do we have any idea what that is going to mean in the number of grants and this dilemma we are facing right now? What is that going to mean?

Dr. ZERHOUNI. At this point I heard the same thing that you heard. So we queried and we asked are there decisions made in our out-year budgets. To this moment, I am not told of any formal decisions that were made by OMB that would imply those cuts in the NIH budget.

Senator HARKIN. I got it from OMB.

Dr. ZERHOUNI. I understand. There were projections, but from the standpoint of our interactions with OMB, we are told that those are projections and estimates that were made, not policy decisions.

Senator HARKIN. Well, I know they are projections. This is what OMB is projecting. I have got the figures right here, a 2 percent cut in fiscal year 2006. That is next year. That is what we are going to be confronting next year, and we are going to be here next year.

So, again, I am just asking. We need some information. What would this mean if OMB's projection goes through and we have this 2 percent cut in fiscal year 2006 and we are confronting that, what does it mean for grants, commitments to researchers, size of

grants? I mean, we need to know what the impact of that is going to be.

Dr. ZERHOUNI. We definitely are willing to provide you with those projections from the standpoint of the agency, and I will provide that to you for the record.

Senator HARKIN. I do not need them right now, but we are going to need them sometime because we are going to start getting into this sometime this year. But we should have some handle on that as to what that might mean, so that we can at least, as we have been saying here, get the facts out as to what this would mean. Before the budget actually comes out is what I am saying, we ought to have this out there so people that are devising the budget know what it is going to mean.

Dr. ZERHOUNI. But again, we checked and those figures are not decisional figures. They are not decisions made. They are projections.

Senator HARKIN. I understand that, but we have got to know what those projections mean in real terms if in fact they follow through on them.

Dr. ZERHOUNI. Definitely.

[The information follows:]

2 PERCENT DECREASE IN FISCAL YEAR 2006

As indicated, while there are mechanically calculated numbers in the OMB computer system that reflect the Administration's overall budget targets in the outyears, no specific funding decisions have been made for NIH or most other domestic programs. In answer to your question, if the NIH budget were to decrease by 2 percent in fiscal year 2006 from the fiscal year 2005 Budget Request, the number of competing research projects grants (RPGs) would decrease by an estimated 2,000 to 2,500 depending on the average cost assumptions used.

Senator HARKIN. Thank you, Dr. Zerhouni. Thank you, Mr. Chairman.

Senator SPECTER. Thank you, Senator Harkin.

OBESITY RESEARCH

Dr. Zerhouni, the issue of obesity is one of enormous importance. In 15 years, obesity has increased by over 50 percent among adults; in 20 years, 100 percent among children and adolescents. We would like a written response as to what can be done by NIH, how this subcommittee might be effective on diet or education. We have both Health and Human Services and Education to try to confront this growing problem.

[The information follows:]

OBESITY RESEARCH

The NIH Obesity Research Task Force, which was established in April 2003 to accelerate research on this escalating health problem, has developed a Strategic Plan for NIH Obesity Research in broad consultation with external scientific and lay experts. We believe that implementation of this Plan is the best way that the NIH can contribute to arresting the obesity epidemic. Combating obesity must be a broad national effort to which the NIH can contribute new and important scientific insights. As noted, the fiscal year 2005 President's Budget request for the NIH reflects a 10 percent increase for obesity research, which would bring total NIH funding for this area to $440 million. The proposed 10 percent increase includes additional new funding to begin implementation of obesity research in specific areas identified in the Strategic Plan because of their scientific opportunity and public health challenge. With respect to your specific reference to diet and education, the

NIH has also recently created a new obesity research website http://www.obesityresearch.nih.gov), which contains links to science-based information generated by many of the NIH Institutes and Centers for the public, patients, and providers. Two helpful programs are the NIDDK's Weight Control Information Network and the NHLBI's Obesity Education Initiative.

MEDICATION TO LOWER PLASMA LIPOPROTEIN (A) [LP(A)]

Senator SPECTER. Last year I asked Dr. Lenfant about research on medication to lower Lp(a). Dr. Alving of the Heart, Lung and Blood Institute, is there anything new that you can inform the subcommittee about on the status of research toward a medication to lower Lp(a)?

Dr. ALVING. Yes. Thank you very much.

Since the past year, there has been no really new information on Lp(a). It is still defined as an emerging risk factor. But there has been certainly very new information on the importance of lowering LDL, even below the guidelines of less than 100 milligrams per deciliter.

Senator SPECTER. We see the LDL research all the time on the front pages.

Dr. ALVING. Yes.

Senator SPECTER. But how about Lp(a)? That has been identified as a very problemsome factor. We have asked you about it repeatedly. What efforts are you making to identify what can be done about it?

Dr. ALVING. The efforts to identify it have been in terms of our ATP III Guidelines Committee, which has been reviewing all of the literature and has been closely focused on the latest guidelines and the latest research.

Senator SPECTER. Aside from reviewing literature, is there active research being undertaken in the field?

Dr. ALVING. There are R01 grants that include Lp(a), but it has not really been able to be classified as a true risk factor. But what I would like to do——

Senator SPECTER. How many grants?

Dr. ALVING. What I would like to do is reply for the record with an actual listing of the R01 grants so that I can give you very specific information about all of our research.

Senator SPECTER. That would be fine. We would appreciate it if you would specify the grants, what they are doing, what their success has been, what more you need to do.

Dr. ALVING. Yes. I will be happy to do that, Senator.

[The information follows:]

RESEARCH ACTIVITIES ON LP(A)

The NHLBI supports a variety of grants and contracts related to the cardiovascular disease (CVD) risks associated with elevated concentrations of Lp(a), factors that influence Lp(a) levels, mechanisms by which Lp(a) may affect CVD, and Lp(a) metabolism. Beginning in 2005, the NHLBI will support measurement of Lp(a) in the next four years of the National Health and Nutrition Examination Survey.

The NHLBI supports the following R01 grants related to Lp(a):

—APEX: Adiposity Prevention by Exercise in Black Girls *(Medical College of Georgia).*

—Biology of Proteolytic Derivatives of Lp(a) *(University of Chicago).*

—Epidemiology of Coronary Artery Calcification *(University of Michigan at Ann Arbor).*

—Genetic Determinants of Lp(a) Concentration *(University of Texas Southwestern Medical Center).*
—Genetic Epidemiology of Blood Lipids and Obesity *(University of Pittsburgh).*
—Lifestyle, Adiposity, and Cardiovascular Health in Youths *(Medical College of Georgia).*
—Macronutrients and Cardiovascular Risk *(Johns Hopkins).*
—Regulation of Lp(a) Metabolism in Humans *(University of California-Davis).*

The Institute also supports a K08 clinical investigator development award for a project on Lp(a), Homocysteine, and Cardiovascular Risk in End-Stage Renal Disease *(Johns Hopkins).*

Lp(a) is a subject in several epidemiologic studies supported through NHLBI contracts:

—Atherosclerosis Risk in Communities Study (ARIC) *(Baylor College of Medicine, Johns Hopkins, Mississippi Medical Center, University of Minnesota—Twin Cities, University of Texas Health Sciences Center, University of North Carolina at Chapel Hill).*
—Cardiovascular Health Study (CHS) *(Johns Hopkins, University of Washington, University of Vermont, University of Pittsburgh, University of California—Davis, University of Wisconsin, Wake Forest University).*
—Coronary Artery Risk Development in Young Adults Study (CARDIA) *(Harbor-UCLA Research and Education Institute, Kaiser Permanente Division of Research, Northwestern University, University of Minnesota—Twin Cities, University of Alabama at Birmingham, University of California—Irvine).*
—Framingham Heart Study *(Boston University Medical Center).*
—Jackson Heart Study *(Jackson State University, Mississippi Medical Center, Tougaloo College).*

Two NHLBI-supported cooperative agreements related to cardiovascular disease risk factors in Alaska Natives and Native Americans also include Lp(a) measurements:

—Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) *(MedStar Research Institute).*
—Strong Heart Study *(MedStar Research Institute, Missouri Breaks Research Inc., Southwest Foundation for Biomedical Research, University of Oklahoma Health Sciences Center, Weill Medical College of Cornell University).*

In 1998, the NHLBI initiated a 4-year Lp(a) Standardization Program to enable accurate and consistent measurement that may help to reconcile various findings. Following completion of the program, a workshop was held to present the new results, evaluate current understanding of Lp(a) as a risk factor for CVD, and design future studies. The workshop report was published in the journal *Clinical Chemistry* in November 2003.

In summary, the following statements can be made with respect to Lp(a).

—In general, research has found only a modest association between Lp(a) levels and CVD risk.
—Compared with plasma LDL, Lp(a) concentrations are relatively resistant to alteration by pharmacologic and lifestyle interventions.
—Lp(a) is a complex and heterogeneous protein, and measurement challenges have created difficulties in comparing data from different sources or assessing the impact of findings on the severity of disease.
—Measurement of Lp(a) is not currently recommended as part of CVD risk assessment in patients.

Senator SPECTER. We are going to try to bring this hearing to a close, following Senator Stevens' admonition. We are keeping a lot of scientists away from their laboratories here and there is a lot of work to be done.

SPINAL MUSCULAR ATROPHY

Dr. Landis, on the issue of spinal muscular atrophy therapeutics, could you bring us up to date on when that will be ready for clinical trials?

Dr. LANDIS. We are actually running three pilot clinical trials right now based on previous data. This is a network that is set up by Susan Iannaccone. In addition, the new project looking at additional compounds is well underway. The advisory committee has created a flow plan, and the first set of awards to come up with

an animal model that would be used for preclinical studies will be awarded in the next week or 2.

In addition, two further solicitations have been put out, one that would that would look for cell culture models again being used to solicit better mechanisms to look at therapeutic molecules, and the second to come up with a satisfactory way to measure the protein that is missing. So I think, between what pilot trials are ongoing and this new therapeutics initiative, we are making significant progress.

Senator SPECTER. Would you supplement your answer with a written report about how you project activities of NIH to proceed in this line looking toward some ultimate answer?

Dr. LANDIS. I would absolutely be pleased to do so.

[The information follows:]

SPINAL MUSCULAR ATROPHY

The NINDS has developed a new program, called the SMA Project, to accelerate the development of therapies for this disease. The SMA Project uses a performance-based, milestone driven, contract mechanism to shorten the cycle time from recognition of a need or opportunity for research to getting research underway on those issues and finding answers. We awarded the primary contract in September 2003. This is an extremely ambitious project in a very challenging area of medical science, and scientific progress is not predictable. However, we have explicitly designed the SMA Project to respond quickly to unanticipated obstacles and to emerging opportunities, in the hopes of achieving our goal of identifying a therapeutic candidate for SMA, and completing the required preclinical research and development by late 2007.

One very important aspect of this program is that we are coordinating the research centrally, calling for targeted research projects to meet specific needs identified by an overall plan, and carefully monitoring progress. The program is guided by a superb Steering Committee, with scientists from academia, industry, the Food and Drug Administration, and the intramural and extramural programs at the NINDS. The Committee has already developed a plan and a sample timeline showing all of the steps necessary to meet the goal of bringing a candidate therapeutic to investigational new drug (IND) status that is necessary for clinical trials, within four years. The sample timeline and other detailed information about this program are available to the public on a website at http://smaproject.org.

A crucial aspect of the SMA Project is the rapid turnaround from identifying a research opportunity or need, to solicitation for research proposals, to funding. The first targeted solicitation for research subprojects, focused on mouse models for testing therapies, was issued in December of 2003. These applications have been reviewed, and expect awards to be issued by June 1, 2004. Two further solicitations were issued in March, on cell culture models and on measuring the crucial protein that is lacking in SMA. Full length proposals are due in May, notification of subcontract awards is scheduled for June and funding for July. These initial proposals have been focused on generating the necessary research tools to identify a candidate treatment that has the highest probability of success in the clinic. Future solicitations will be aimed at stimulating new drug identification; the development of gene therapy; and establishing centralized testing facilities to conduct the activities required in the flow plan, such as evaluating compounds in animal and cellular models of SMA.

In addition to the contract-based SMA therapeutics development project, we are currently supporting the short term, open label pilot clinical trials, being conducted by Dr. Iannaccone, of three drugs that have shown promise either in patients or in models of SMA. We will be looking to see if these results warrant larger trials. We are also planning a workshop on clinical trials for SMA to be held later this year. This workshop is intended to ready the SMA clinical community to test interventions that result from the SMA Project, by promoting collaboration and high quality trial design. In preparation, we are moving forward to work with the community on identifying and evaluating drugs now available that may slow the progression of SMA and be ready for testing in clinical trials.

So, we are exploiting the best existing opportunities in the short term for slowing the disease, and at the same time we are developing the best possible treatments for the future through the SMA Project. Finally, I want to emphasize that the SMA

Project is not replacing our traditional investigator-initiated grant programs and our intramural program on SMA; we are continuing to support this research as well. We also have extensive research programs in cross-cutting areas such as gene therapy, drug screening, and stem cells that may ultimately have an impact on SMA.

Senator SPECTER. Thank you. Dr. Spiegel, in your field we had a high visibility attention-getter when NBA basketball star Alonzo Mourning was seeking a kidney transplant and was forced to retire early on glomerular disease that damages filters in the kidney that cleanse the blood. We were asked to hold a separate hearing which was just too much to do. Could you give us an update on where that stands?

Dr. SPIEGEL. Yes, Senator, I would be happy to do that.

The glomeruli are tiny units that cleanse the blood in the kidney and they are comprised of kidney membranes and small capillary blood vessels. There are really two types of injuries that occur. One is glomerulonephritis, which is caused by the immune system. Many institutes at NIH work together to direct attention to preventing kidney failure from glomerulonephritis.

The form that you are referring to, focal segmental glomerulosclerosis, affects children, and as you implied in the case of Alonzo Mourning, can affect African Americans disproportionately. We have intensive research efforts together with patient advocacy groups such as the NephCure Foundation. In fact, we have launched a clinical trial directed at new and more effective therapies for this important disorder, and we are hopeful that from that trial, new, safer, and more effective medication will emerge. But at the same time, we are also reinforcing our basic research to understand the basis for the injury that occurs in glomerulosclerosis.

Senator SPECTER. Thank you very much.

AGE-RELATED MACULAR DEGENERATION (AMD)

Dr. Sieving, with respect to macular degeneration, how are you moving ahead on the clinical trial networks for advancing AMD research?

Dr. SIEVING. AMD is a leading cause of vision loss and, in fact, one of the leading causes of disability in the elderly. It is a neurodegenerative disease. A part of the mission of the institute is to form alliances, scientific alliances and communication related to other neurodegenerations, including Parkinson's and Alzheimer's disease, because there are some common features that mutually these two multiple areas can learn.

Now, the AMD network specifically is going to tackle the opportunities presented by existing and new compounds to modify the effects of and the course of AMD. One such opportunity—it is not actually a network, but one recent success came from the finding reported about a year ago that antioxidant nutrients and zinc can decrease the risk of progressing to end-stage vision loss. That is a very important finding in the aggregate for the American population. Now it is our task to take that bedside finding back to the bench to help understand on a molecular and cell biological basis why this is happening.

Back on the AMD networks, we are proceeding with that. Applications are coming in, will be reviewed, and we hope that we will be able to successfully fund this venture.

AUTISM RESEARCH

Senator SPECTER. Dr. Insel, with respect to autism, could you bring us up to date on the research activities of your department and what success you have had and what your projection is for the future?

Dr. INSEL. I would be happy to, Senator.

We have in the past year launched a total of eight STAART centers. These are interdisciplinary centers to bring both a research effort and an intervention effort to autism. This is a program that will go over the next 4 to 5 years. It involves five of the institutes that are here today. It is, we think, a great national effort that will, by coordinating efforts across many different sites, lead to some very new insights into this troubling and still very mysterious illness.

Senator SPECTER. We have quite a number of questions for the record. We very much appreciate your coming. We appreciate even more the outstanding work you are doing. We are committed to doing our utmost to help you on the funding. When the other research entities come forward with their requests, it continues to be my view that it is a very, very solid capital investment for the United States and we will continue to push on all lines.

Anything further, Senator?

SPINAL MUSCULAR ATROPHY (SMA)

Senator HARKIN. Yes, just one thing, Mr. Chairman.

Dr. Landis, on the SMA issue and what you are sending up to us, I tried to listen to your answer, but would you also look ahead as to how soon we might be going to clinical trials, and what the—I hate to use the word "Roadmap" but what that time line might be?

Dr. LANDIS. We would be pleased to do that. The projection is 4 years for this new initiative to come to fruition with optimally selected compounds, but I will certainly give you a detailed answer.

Senator HARKIN. I will take a look at that.

TRANS-NIH OBESITY TASK FORCE

Back on the issue of obesity, I met with Dr. Gerberding last week at CDC. They have said that now it may be surpassing tobacco usage as the biggest health menace that we face as Americans. Again, I am wondering how, Dr. Zerhouni, you are approaching this in terms of NIH's role in looking at obesity.

Again, it always seems to me that it is easier for people who have never been obese to not be obese than it is for someone who becomes obese to lose weight and hold it down. That is just the facts.

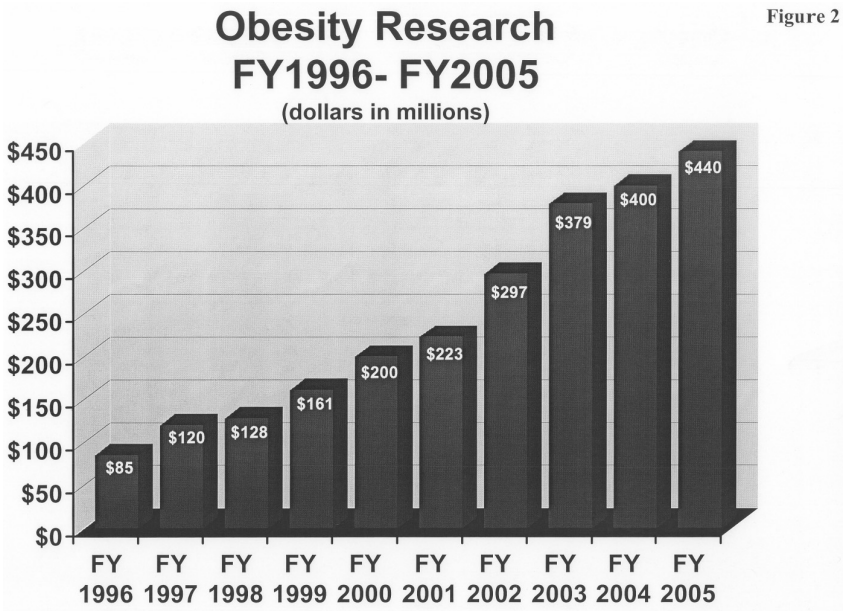
So how do we prevent it in the first place? It seems to me that one of the links in child health, Dr. Alexander, as kids develop and as they learn and grow—it seems to me some research ought to be done on that, what hkids eat and how they develop. And there may be some genetic problems too. I do not know. Dr. Collins could be involved in that.

I guess what I am getting at is this seems to lend itself to some kind of an inter-institute kind of task force to look at how we get

to the prevention end of it, not just to the cure, but what are some of the forces that might go into preventing this in the first place.

Dr. ZERHOUNI. You are absolutely correct, Senator. As I indicated to you in the past through this graph, NIH started investing in obesity 10 years ago. But more importantly is the relevancy of the question you are asking. Last year I asked that we form a trans-NIH Obesity Task Force that is led by Dr. Spiegel. This year we are going to increase funding in obesity research by 10 percent. Here on the screen I can actually show you what that 10 percent is going to be related to [see figure 3]: $3.5 million will be the prevention and treatment of childhood obesity in primary care settings; $3.5 million will be site-specific approaches to prevent and treat pediatric obesity.

Figure 2



Obesity Initiative **Figure 3**

Total increases 10% from $400M in FY 2004 to $440M in FY 2005

Of this:

* $22 million increase, follows recommendations of Trans-NIH Obesity Task Force.

1. $3.5M -- Prevention and Treatment of Childhood Obesity in Primary Care Settings
2. $3.5M -- Site-Specific Approaches to Prev./Treat. of Pediatric Obesity
3. $6M -- Neurological Basis of Obesity
4. $2.0M -- Bioengineering Approaches for Prev./Treat. of Overweight and Obesity
5. $1M -- Obesity and the Build Environment
6. $6M -- Obesity Clinical Research Center

In a nutshell, we are going to focus on the aspects of prevention and understanding the evidence that we need to, in fact, stop the leading edge of the epidemic which is, we agree, in childhood. The earlier we intervene, the more likely we are to dampen the epidemic as we see it. So we are focusing those efforts exactly on that. We are widening our portfolio. We have quadrupled our investment on obesity research because we knew already a while back that it would become a public health problem.

In addition to that, the other part of the new plan, which is on the web site, is receiving public comment, which is related to exactly what you are asking, this trans-NIH view, the other end of the spectrum is most of the diseases that are developed because of obesity are what we call comorbidities, diabetes, hypertension. Those are the ones that really hit the patients hard. Those do not occur to the same degree at every level of overweight. They occur disproportionately in the very morbid, high obesity patient with a BMI index of 33, 34, 35. So the other component of our strategy is to look at the front end, children, and look at those who are very likely to develop the co-morbidities and understand how you stop obesity from giving diabetes to patients and what is the relationship there, what is the relationship with hypertension, and so on.

Dr. Spiegel, who is leading the trans-NIH task force, will be happy to provide you more detailed information. But we agree with you. It is a multi-prong strategy that we need to implement across all Federal Departments and NIH needs to attack now the leading edge and the trailing edge of what we know are the most important points of action that we should take.

Senator HARKIN. Well, I appreciate it. From my own standpoint, it is the leading edge is where you ought to focus. I hope what I am not hearing, Mr. Chairman, is that somehow or other we are

going to do research into finding out how you can be obese, but we can have some kind of blockers to keep you from getting diabetes. I think more research ought to be into the front end to keep you from getting obese in the first place. That is my unscientific statement on that.

Thank you.

Dr. ZERHOUNI. Thank you, Senator.

Senator SPECTER. Thank you, Senator Harkin. Thank you all very much.

PREPARED STATEMENT RECEIVED

We have received the prepared statement of Senator Mary L. Landrieu which will be placed in the record.

[The statement follows:]

PREPARED STATEMENT OF SENATOR MARY L. LANDRIEU

Thank you, Mr. Chairman. Thank you, Dr. Zerhouni, for joining us today to discuss the National Institutes of Health (NIH) and its 2005 budget, as proposed by the President. The National Institutes of Health are an integral component to our nation's health and safety. Within the twenty-seven Institutes and Centers at the National Institutes of Health, research is being conducted and studies are beginning to show, new and exciting ways to prevent, detect, diagnose, and treat the diseases and disabilities which plague our country and the world. Fostering communication and collaboration, the National Institutes of Health provide grant and research opportunities to universities, medical schools, hospitals, and other research institutes in addition to conducting their own federal research. Through these collaborations, the National Institutes of Health position themselves as the world's foremost medical research center and the focal point for domestic medical research.

The President's fiscal year 2005 budget request provides $28.8 billion for the National Institutes of Health. This number represents an increase of $764 million, or 2.7 percent, over fiscal year 2004 levels. As a member of the Senate Appropriations Subcommittee on Labor, Health, Human Services and Education, I was proud to lend my support to doubling the National Institutes of Health budget in just five years. By steadfastly keeping the National Institutes of Health funding on track, my colleagues and I enabled the National Institutes of Health to support far more promising research than it was ever able to before, and to advance into new areas of science. While I am very proud of this aggressive increase and commitment to funding, we must not fall back on our commitment to medical research.

Research at the National Institutes of Health has a real and direct impact on my state of Louisiana. The Centers for Disease Control and Prevention (CDC) reports that 9,306 people have been affected by the West Nile Virus in the United States this year. 240 of those infected have died. Of those cases, the state of Louisiana has reported 123 cases and 8 deaths this year. Mosquito-borne diseases, such as the West Nile Virus, represent one of the most serious and preventable public health threats for many states. With the recent outbreak of the West Nile Virus in the United States, the National Institute of Allergy and Infectious Diseases at the National Institutes of Health have accelerated their research efforts into the West Nile Virus, possible vaccines, and treatment options. We have not yet developed a vaccine to combat the West Nile Virus but with the proper funding, researchers at NIH are committed to finding one.

In addition to West Nile, Louisianians also find themselves battling another deadly epidemic, obesity. Currently in the United States there are 127 million adults that are overweight, 60 million of whom are obese, and 9 million who are severely obese. For children ages 6–11, 30.3 percent are overweight and 15.3 percent are obese. These numbers have more than doubled in the last thirty years. This epidemic threatens the health of our Nation and increases the incidence of type 2 diabetes, fatty liver disease, kidney failure, as well as many other diseases. I am pleased to learn that the fiscal year 2005 budget for the National Institutes of Health supports an expansion of $40 million to its obesity research portfolio but this is not nearly enough to reverse a trend of this magnitude. I hope that we can do more in the near future to end this epidemic. It is imperative that we work to understand the neurobiological, genetic, behavioral, and environmental basis of obesity and develop strategies to maintain healthy weight in adults and children.

In conclusion, I would like to speak briefly about the flu epidemic that has recently taken a toll on our country and the global community. The CDC estimates that 10–20 percent of Americans come down with the flu each year. Of these numbers, more than 100,000 people are hospitalized and approximately 36,000 Americans die from the flu and its complications each year. While we have not experienced a flu pandemic since 1968, each fall and winter brings with it a new strain of the flu. Research institutions and health departments around the world are cooperating to track flu outbreaks and to determine the many different types, strains, and causes. The National Institute of Allergy and Infectious Diseases (NIAID) at NIH currently supports research into how the flu virus works and into developing better vaccines to prevent and treat the infection. By supporting this research at NIH we can hope to better track the development of flu strains and arm ourselves with the proper vaccines and treatments that will prevent deadly outbreaks.

While these are but a few examples of the impact of NIH research on the state of Louisiana, I think they make it clear that the research being funded through the National Institutes of Health has a real and immediate impact on the citizens of our country. By wisely investing in medical research that advances the prevention and treatment of diseases, we in fact are saving money that would otherwise have to be used to diagnose and treat these diseases. I know that my colleagues agree that funding a cure is perhaps the best use of government resources there is. It is my hope that we will continue to increase the National Institutes of Health budget so that our children and grandchildren can truly benefit from the cures and medical advances made every day at NIH.

ADDITIONAL COMMITTEE QUESTIONS

Senator SPECTER. 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 BY SENATOR HERB KOHL

OBESITY

Question. Dr. Crawford, both USDA and FDA have recently announced new efforts to combat the increasing problem of obesity. FDA announced the "Calories Count" program, and USDA has money in several programs, including WIC, to help battle this problem. However, for all of the government's efforts, all of the money being put into this effort pales in comparison to the food industry's billions of dollars worth of advertising. How can the government successfully get its message out when, at first glance, its efforts appear to be dwarfed by the food industry? How do your agencies compete with that?

Answer. In support of the President's Healthier U.S. initiative, the DHHS established a complementary initiative, Steps to a Healthier U.S., which emphasizes personal responsibility for the choices Americans make for healthy behaviors. One aspect of this initiative focuses on reducing the major health burden created by obesity and other chronic diseases. Following DHHS' July 2003 Roundtable on Obesity and Nutrition, on August 11, 2003, FDA established an Obesity Working Group, or OWG, to prepare a report that outlines an action plan to cover critical dimensions of the obesity problem from FDA's perspective and authorities. This report was released on March 12, 2004.

There is no simple answer to the problem of obesity. Achieving success in reducing and avoiding obesity will occur only as a result of efforts over time by individuals as well as various sectors of our society. It should be noted, however, that most associations, agencies, and organizations believe that diet and physical activity should be addressed together in the fight against overweight and obesity.

The OWG report provides a range of short and long-term recommendations to address the obesity epidemic with a focus on a "calories count" emphasis for FDA actions. These recommendations are based on sound science and address multiple facets of the obesity problem under FDA's purview, including developing appropriate and effective consumer messages to aid consumers in making wiser dietary choices; establishing educational strategies and partnerships to support appropriate messages and teach people, particularly children, how to lead healthier lives through better nutrition; developing initiatives to improve the labeling of packaged foods with respect to caloric and other nutrition information; encouraging and enlisting

restaurants in efforts to combat obesity and provide nutrition information to consumers, including information on calories, at the point-of-sale; developing new therapeutics for the treatment of obesity; designing and conducting effective research in the fight against obesity; and continuing to involve stakeholders in the process.

Regarding food labeling, the OWG report contains several recommendations based on sound science. I will provide these recommendations for the record.

[The information follows:]

Publish an advance notice of proposed rulemaking, or ANPRM, to seek comment on the following:

—How to give more prominence to calories on the food label, for example, increasing the font size for calories, including a column in the Nutrition Facts panel of food labels for percent Daily Value for total calories, and eliminating the listing for calories from fat;

—Whether to authorize health claims on certain foods that meet FDA's definition of "reduced" or "low" calorie. An example of a health claim for a "reduced" or "low" calorie food might be: "Diets low in calories may reduce the risk of obesity, which is associated with type 2 diabetes, heart disease, and certain cancers."

—Whether to require additional columns on the Nutrition Facts panel to list quantitative amounts and percent Daily Value of an entire package on those products and package sizes that can reasonably be consumed at one eating occasion—or declare quantitative amounts and percent Daily Value of the whole package as a single serving if it can reasonably be consumed at a single eating occasion; and,

—Which, if any, reference amounts customarily consumed of food categories appear to have changed the most over the past decade and hence require updating.

In addition, FDA will file and respond in a timely way to petitions the agency has received that ask FDA to define terms such as "low," "reduced," and "free" carbohydrate; and provide guidance for the use of the term "net" in relation to carbohydrate content of food—these petitions were filed on March 11, 2004.

FDA will also encourage manufacturers to use dietary guidance statements, an example of which would be, "To manage your weight, balance the calories you eat with your physical activity." In addition, the Agency will encourage manufacturers to take advantage of the flexibility in current regulations on serving sizes to label as a single-serving those food packages where the entire contents of the package can reasonably be consumed at a single eating occasion and encourage manufacturers to use appropriate comparative labeling statements that make it easier for consumers to make healthy substitutions.

FDA believes that if the report's recommendations are implemented they will make a worthy contribution to confronting the nation's obesity epidemic and helping consumers' lead healthier lives through better nutrition.

FDA also believes that the regulatory scheme for claims in food labeling, whether health claims, nutrient content claims, or other types of claims, are science based, and we continue to consider modifications to our regulations to keep up with recent scientific developments. A benefit of standardized, science-based terminology, as with other terms that FDA has defined that consumers may use to make health-based dietary choices—e.g., terminology concerning fat content—is that it allows consumers to compare across products and it encourages manufacturers to compete based on the nutritional value of the food. However, FDA does not regulate television and other media marketing of food products. Some of the modifications FDA is currently considering are described above in the list of topics to be covered by the ANPRM the agency intends to issue.

With respect to conveying the report's messages to the public, FDA believes that all parties, including the packaged food industry, restaurants, academia, and other private and public sector organizations in addition to government agencies at all levels, have an essential role to play. On April 22, 2004, FDA's Science Board focused on specific recommendations from the OWG report. These recommendations call on FDA to work through a third-party facilitator to engage all involved stakeholders in a dialogue on how best to construct and convey obesity messages in the restaurant setting and in the area of pediatric obesity education.

This approach is one example of how the Agency intends, by means of public and private partnerships, to leverage its ability to convey appropriate messages on obesity to the public with the goal of changing behavior and ultimately reversing obesity trends in the United States.

IMPORT INSPECTIONS

Question. Dr. Crawford, the FDA budget this year includes a $7 million increase to fund 97,000 food import examinations. This is a big increase in inspections over any previous year—still, however, less than one percent of all of the food imported into this country will be inspected. How would you respond to charges that you still aren't inspecting nearly enough imported food, especially in light of events during the past year where bad food has gotten in and people have died? How do we ensure consumers that their food is indeed safe?

Answer. FDA is appreciative of the additional funding we have received for the inspection of domestic firms and for inspections of imported foods. FDA believes it is more effective to focus our resources in a risk-based manner than to focus simply on increasing the percentage of imported food shipments that are physically inspected. It is important to note that every shipment of FDA-regulated food which is entered through Customs and Border Protection as a consumption entry is electronically reviewed by FDA's Operational and Administrative System for Import Support to determine if it meets identified criteria for further evaluation by FDA reviewers and physical examination and/or sampling and analysis or refusal. This electronic screening allows FDA to concentrate its limited inspection resources on high-risk shipments while allowing low-risk shipments to proceed into commerce.

Due to constantly changing environments of operation, e.g., counterterrorism and BSE, our domestic inspection and import strategy cannot be defined in terms of a percentage of coverage through inspections, physical examinations and sample analyses. It needs to be a flexible blend of the use of people, technology, information and partnerships to help protect Americans from unsafe imported products. Accordingly, the Agency is developing and using strategies for mitigating risks prior to importation through partnerships and initiatives based on best practices and other science based factors relevant to the import life cycle, i.e., from foreign manufacturer to the U.S. consumer. Recently this principle has been applied in the "Canadian Facility Voluntary Best Management Practices for Expediting Shipments of Canadian Grains, Oilseeds and Products to the United States" implemented February 24, 2004, and designed to mitigate the potential of mammalian protein prohibited from being fed to cattle or other ruminants under BSE-prevention regulations promulgated by CFIA and FDA.

Another piece of the long term solution to a higher level of confidence in the security and safety of food products lies in information technology that will merge information on products and producers with intelligence on anticipated risks to target products for physical and laboratory examination or refusal. This strategy would rely on data integrity activities that reduce the opportunity for products to be incorrectly identified at ports. It would also rely on cooperation from producers so that FDA can identify sources that are unlikely to need physical testing. However, even with such targeting, improvements are limited by the available methodologies for assessing threat agents and our ability to predict which tests ought to be used.

We are ramping up our food inspections, but we recognize that we also need to inspect smarter, not just inspect more. That is why FDA is making significant investments in technology and information resources such as the development of the Mission Accomplishment and Regulatory Compliance Services System, MARCS. MARCS is a comprehensive redesign and reengineering of two core mission critical systems at FDA: FACTS and the Operational and Administrative System for Import Support, OASIS. OASIS supports the review and decision making process of products for which entry is sought into the United States. We are using funds to work to further improve targeting and using force multipliers such as IT.

FDA also has a proof of concept project, called "Predict," with New Mexico State University under a Department of Defencse contract which is being designed to enhance agency capability to rapidly assess and identify import entries based on risk using relevant information from various sources including regulated industry, trade, other federal, State, and local entities, and foreign industry and governments. This project, if successful, will greatly enhance FDA's capability to be smarter in directing field activities on products of greater risk to public health and safety. The proof of concept project is projected to be completed in the Fall of 2004. The relentless growth in the volume of domestic as well as imported food products, which are increasingly in "ready for consumer sale packaging." Food imports are now growing at 19 percent per year. FDA needs to use all the potential tools available to improve its efficiency in food security and safety coverage.

In addition, FDA has several strategic initiatives to enhance safety. One of these is "Agency Initiatives to Improve Coverage," which includes the creation of the Southwest Import District to better coordinate import activities on the southern border. Another is reciprocal FDA and U.S. Customs and Border Protection training to

improve product integrity of goods offered for import and increase enforcement actions by Customs to deter willful violations of U.S. laws and regulations. While foreign inspections and border operations provide some assurance that imported foods are safe, the agency continues to work to foster international agreements and harmonize regulatory systems. For instance, we actively participate in the Canada/U.S./Mexico Compliance Information Group, which shares information on regulatory systems and the regulatory compliance status of international firms to protect and promote human health.

It is very important that American consumers trust the safety of the food supply. FDA has made fundamental changes in how we implement our mission of protecting the food supply, so that all Americans can have confidence that their food has been handled under secure conditions that provide assurance of its safety.

FDA FOIA POLICIES

Question. Dr. Crawford, my office has been working with a non-profit patient advocacy group, the TMJ Association, in their efforts to have two FOIA requests that are well over a year old responded to. Their original FOIA request was made on November 1, 2002 (request number 02017071), more than 17 months ago, and the subsequent request was made on March 25, 2003 (request number 03004361). They have not yet received the information requested, and have been unable to get a date commitment by FDA as to when the information will be provided. It is my understanding that they have been informed that FOIA requests are severely backlogged, and the FDA has no idea when they will be able to process their request. What is the current backlog for FOIA requests?

Answer. As of April 28, 2004, FDA has 19,369 pending FOIA requests—17,555 have been pending more than 20 days and 1,814 have been pending 20 days or less. The Denver District Office is responsible for responding to the two requests from the TMJ Association. As of April 28, 2004, Denver District Office has 369 pending FOIA requests—357 requests have been pending more than 20 days, and 12 requests have been pending 20 days or less.

Question. How many FDA staff are responsible for handling these requests? Is this their sole responsibility, or do they have other responsibilities as well?

Answer. For fiscal year 2003 the total number of personnel responsible for processing FOIA requests was 91 FTE, 75 full time employees, and 16 FTE work years representing personnel with part-time FOIA duties in addition to other responsibilities.

Question. Does FDA need additional staff or resources in order to process these requests on a timely basis?

Answer. In some agency components FOIA is a collateral duty. For example, in most FDA field offices, Compliance Officers whose primary responsibilities are related to the Agency's regulatory enforcement activities also perform FOIA duties as permitted by time and regulatory workload. Additional staff devoted to FOIA could shorten the amount of time for processing requests.

Question. What do you believe is a reasonable length of time for a group to wait for an information request to be processed and responded to?

Answer. Requests are processed by the agency component that maintains the requested records. There are a number of factors that must be considered in order to predict a reasonable amount of time for a request to be processed. Those factors include the volume of requests received by the component, the complexity of requests received, the amount of time required to search for records, the amount of time require to review the records to determine whether information is releasable under FOIA, and the resources available to process requests.

Question. What is the average length of time it takes to process a FOIA request? Can you please explain the severe delay in processing this specific one, which has taken over two years and apparently has no end in sight? Can you please provide me a timeframe within which the FDA will respond to these two particular FOIA requests?

Answer. Under the Electronic Freedom of Act Amendments of 1996, agencies are permitted to establish multiple tracks for processing FOIA requests based on the complexity of the requests and the amount of work and time required to process requests. Some FDA components have established multiple processing tracks. Requests are processed on a first in, first out basis within each track. The median number of days to process requests in the simple processing track is 19 days. The median number of days to process requests in the complex processing track, for more complicated requests, is 363 days. For requests that are not processed in multiple processing tracks, the median number of days to process is 44 days.

Due to a heavy load of regulatory cases in the Denver District Office that must be handled by the Compliance Officers in addition to staff shortages, FOIA work in the Denver District is being performed by one individual on a part-time basis. This has resulted in a significant backlog of FOIA requests. The Denver District Office expects to fill request 02–17071 from the TMJ Association in six months, and request 03–4361 in one month.

Question. What additional efforts can this group undertake in order to speed up their request?

Answer. The Denver District Office expects to fill request 02–17071 from the TMJ Association in six months, and request 03–4361 in one month.

In addition, the Denver District is reviewing and evaluating its FOIA workload and will develop a strategy aimed at reducing the backlog of FOIA requests.

Question. What is the FDA's policy on charging for FOIA requests made by non-profit patient advocacy groups?

Answer. The FOIA sets forth criteria that agencies must follow with respect to charging for processing FOIA requests. Non-profit organizations are considered Category III requesters. Such requesters receive 100 pages of duplication and two hours of search at no charge. If the number of pages exceed 100 and/or if the amount of search time exceeds two hours, Category III requesters are charged based on the FOIA fee schedule of the Department of Health and Human Services. The fee for duplication is $.10 per page, and the fee for search is based on the grade level of the individual who processes the request. I will be happy to provide the current grade rates for the record.

[The information follows:]

CURRENT GRADE RATES

GS–1 through 8—$18.00 per hour
GS–9 through 14—$36.00 per hour
GS–15 and above—$64.00 per hour

In addition, requesters may make a request for waiver or reduction of fees if their request meets the following criteria: disclosure of the information is in the public interest because it is likely to contribute significantly to public understanding of the operations or activities of the Government; and, disclosure is not primarily in the commercial interest of the requester.

IMPLICIT PRE-EMPTION

Question. Adverse reactions to prescription drugs and other medicines take the lives of more than 100,000 Americans each year, and millions more are seriously injured. For many years, state tort laws have enabled some victims to receive compensation for their injuries. It has been brought to my attention that the Food and Drug Administration (FDA) has stepped in to protect drug companies from liability in some of these lawsuits, potentially robbing individuals of their only means of compensation. FDA's actions are even more troubling when you consider that these lawsuits have other important purposes, such as deterring future bad behavior and providing the American public with access to important health and safety information. How many times has the FDA interfered in lawsuits, arguing that implicit preemption prohibits a plaintiff from receiving compensation for their injuries? In how many of these cases has a court held that the plaintiff's tort claim was implicitly pre-empted by federal law?

Answer. In the past several years, the Department of Justice (DOJ) has represented the United States in four cases involving state-law challenges to the adequacy of FDA-approved risk information disseminated for FDA-approved new drugs.[1] In each case, DOJ contended that the state-law claim was preempted by federal law. In addition, in some cases, DOJ argued that the state-law claim was not properly before the court by operation of the doctrine of primary jurisdiction.[2]

The legal basis for preemption in these cases is FDA's careful control over drug safety, effectiveness, and labeling according to the agency's comprehensive authority under the FDCA and FDA implementing regulations. If state authorities, including judges and juries applying state law, were permitted to reach conclusions about the

[1] FDA also periodically becomes involved, through the Department of Justice, in cases involving preemption of state-law requirements under the medical device provisions of the FDCA, which include an express preemption provision, 21 U.S.C. 360k(a).

[2] Primary jurisdiction allows a court to refer a matter to an administrative agency for an initial determination where the matter involves technical questions of fact and policy within the agency's jurisdiction. See, e.g., *Israel* v. *Baxter Labs., Inc.*, 466 F.2d 272, 283 (D.C. Cir. 1972); see also 21 CFR 10.60.

safety and effectiveness information disseminated with respect to drugs for which FDA has already made a series of regulatory determinations based on its considerable institutional expertise and statutory mandate, the federal system for regulation of drugs would be disrupted. I will be happy to include information on the four cases for the record.

[The information follows:]

Bernhardt

In 2000, two individual plaintiffs filed product liability actions in a New York court against Pfizer, Inc., seeking a court order requiring the company to send emergency notices to users of the prescription antihypertensive drug CARDURA (doxazosin mesylate) and their physicians. The notices would have described the results of a study by a component of the National Institutes of Health (NIH) that, the plaintiffs alleged, demonstrated that Cardura was less effective in preventing heart failure than a widely used diuretic. FDA had not invoked its authority to send "Dear Doctor" letters or otherwise disseminate information regarding a drug that the agency has determined creates an "imminent danger to health or gross deception of the consumer." (21 U.S.C. 375(b).) The plaintiffs, nevertheless, filed a lawsuit under state common law seeking relief that, if awarded, would have pressured the sponsor to disseminate risk information that FDA itself had not disseminated pursuant to its statutory authority.

FDA's views were submitted to the federal district court in the form of a Statement of Interest.[3] The Statement relied on the doctrine of primary jurisdiction. The Statement also took the position that the plaintiffs' request for a court order requiring the dissemination of information about NIH study results to users and prescribers of CARDURA was impliedly preempted. According to the Statement, the court order "would frustrate the FDA's ability effectively to regulate prescription drugs by having the Court substitute its judgment for the FDA's scientific expertise." The Statement also noted that, if the court granted the requested order, a direct conflict would be created between the information required to be disseminated by the court and the information required to be disseminated by FDA under the FDCA (in the form of the FDA-approved labeling).

The Statement contended that state law could not provide a basis for requiring a drug manufacturer to issue drug information that FDA had authority to, but did not, require. Importantly, the submission did not argue that the state-law claim was preempted because FDA had reached a determination that directly conflicted with the plaintiff's view. Nor did it assert that FDA had specifically determined that the information on the NIH study requested by the plaintiffs was unsubstantiated, false, or misleading. In this sense, the Statement of Interest in Bernhardt was the most aggressive, from a legal perspective, than the three subsequent DOJ submissions on FDA's behalf in preemption cases made during the present Administration.

The United States District Court for the Southern District of New York accepted the primary jurisdiction argument made on FDA's behalf. (*Bernhardt* v. *Pfizer, Inc.*, 2000 U.S. Dist. LEXIS 16963, *9 (whether the additional warnings sought by the plaintiffs were appropriate "is a decision that has been squarely placed within the FDA's informed expert discretion")). It did not address the preemption issue. The case was voluntarily dismissed on April 22, 2003.

Dowhal

In 1998, an individual plaintiff in California asked that State's attorney general to initiate an enforcement action against SmithKline Beecham and other firms marketing OTC nicotine replacement therapy products in California. (These products are marketed pursuant to an approved new drug application.) The plaintiff contended that the FDA-approved warnings for the defendants' products did not meet the requirements of a state statute called the Safe Drinking Water and Toxic Enforcement Act (Cal. Health & Safety Code § 25249.5 et seq.), also known as Proposition 65. From 1996 through 2001, FDA had repeatedly advised the defendants that they could be liable under the FDCA for selling misbranded products if they deviated from the FDA-approved warning labeling for their products. FDA also advised the state attorney general in writing in 1998 that the defendants' warning in the labeling clearly and accurately identified the risks associated with the products and, therefore, met FDA requirements under the FDCA. After receiving the letter, the attorney general declined to initiate enforcement action.

Nevertheless, in 1999, the individual plaintiff initiated a lawsuit of his own in California state court under Proposition 65's "bounty-hunter" provision, which em-

[3] Statement of Interest of the United States; Preliminary Statement, *Bernhardt* v. *Pfizer, Inc.*, Case No. 00 Civ. 4042 (LMM) (S.D.N.Y. filed Nov. 13, 2000).

powers individuals to file enforcement actions under that statute on behalf of the people of the State of California. The lawsuit asked the court to award civil money penalties and restitution, and to issue an injunction requiring the defendants to disseminate warnings for their products that differed from the warnings required by FDA. In 2000, the plaintiff filed a citizen petition with FDA requesting that the agency require the defendants to change their warnings to reflect the language sought by the plaintiff in the lawsuit. FDA rejected the proposed language, determining that it lacked sufficient support in scientific evidence and presented a risk of mischaracterizing the risk-benefit profile of the products in a way that threatened the public health. Although the trial court found for the defendant, the California Court of Appeal rejected the defendant's contention that the plaintiff's claim was preempted under the FDCA, and allowed the lawsuit to proceed. (*Dowhal* v. *SmithKline Beecham Consumer Healthcare,* 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002), argued, Case No. S–109306 (Cal. Feb. 9, 2004).)

FDA's views were presented to the Court of Appeal of California in an amicus curiae ("friend of the court") brief and to the Supreme Court of California in a letter brief and an *amicus* brief.[4] All three documents explained that the warning language sought by the plaintiffs had been specifically considered and rejected by FDA as scientifically unsubstantiated and misleading. Including the language would, therefore, misbrand those products and cause the defendants to violate the FDCA. The documents explained, further, that principles of conflict preemption applied to the plaintiffs' claim because it was impossible for defendants to comply with both federal and state law and because the state law posed an obstacle to the accomplishment of the full purposes and objectives of the FDCA.

The California Court of Appeal rejected the preemption argument. (*Dowhal* v. *SmithKline Beecham Consumer Healthcare,* 2002 Cal. App. LEXIS 4384, ***16–17 (Cal. Ct. App. 2002) (reversing trial court decision granting summary judgment for defendants on preemption grounds)). On April 15, 2004, the California Supreme Court reversed the appeals court decision, finding a direct conflict between FDA requirements and the state-law warning requirement advocated by the plaintiff. (*Dowhal* v. *SmithKline Beecham Consumer Healthcare,* 2004 Cal. LEXIS 3040.)

Motus

Also in 2000, an individual plaintiff sued Pfizer in a California court alleging, among other things, that the company had failed to fulfill its state common law duty to warn against the risk of suicide the plaintiff alleged was presented by ZOLOFT (sertraline HCl), an FDA-approved drug in the selective serotonin reuptake inhibitor (SSRI) class indicated to treat depression (among other things). On numerous occasions, FDA had specifically considered and rejected such language for SSRIs as scientifically unsupportable and inconsistent with FDA determinations as to the safety and effectiveness of the products.

The United States District Court for the Central District of California (to which the case had been removed on the ground of diversity) rejected the defendant's preemption argument, allowing the lawsuit to proceed. (*Motus* v. *Pfizer Inc.*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000).) The court later granted the defendant's motion for summary judgment on non-preemption grounds (196 F. Supp. 2d 984, 986 (C.D. Cal. 2001)), and the plaintiff appealed. DOJ submitted an amicus curiae brief to the United States Court of Appeals for the Ninth Circuit on FDA's behalf.[5] The brief's arguments were essentially the same as the arguments advanced in *Bernhardt.* In contrast to the situation in *Bernhardt,* however, in Motus, FDA had specifically considered, and rejected, the language requested by the plaintiff under state law. The appeals court affirmed the trial court's decision earlier this year (2004 U.S. App. LEXIS 1944 (9th Cir. February 9, 2004)).

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[4] Letter from Robert D. McCallum, Jr., Ass't Attorney General, *et al.*, to Frederick K. Ohlrich, Supreme Court Clerk/Administrator, Dowhal v. SmithKline Beecham Consumer Healthcare LP, *et al.*, Case No. S–109306 (Cal. filed Sept. 12, 2002); Amicus Curiae Brief of the United States of America in Support of Defendants/Respondents SmithKline Beecham Consumer Healthcare LP, *et al.*, *Dowhal* v. *SmithKline Beecham,* Case No. A094460 (Cal. Ct. App. filed Mar. 22, 2002); Amicus Curiae Brief of the United States of America in Support of Defendants/Appellants SmithKline Beecham Consumer Healthcare LP, et al., *Dowhal* v. *SmithKline Beecham,* Case No. S109306 (Cal. filed July 31, 2003).

[5] Amicus Brief for the United States in Support of the Defendant-Appellee and Cross-Appellant, and in Favor of Reversal of the District Court's Order Denying Partial Summary Judgment to Defendant-Appellee and Cross-Appellant, *Motus* v. *Pfizer,* Case Nos. 02–55372 & 02–55498 (9th Cir. filed Sept. 3, 2002).

In re PAXIL

In 2001, individuals filed suit in a California court on behalf of past or current users of PAXIL (paroxetine HCl) against the drug's manufacturer, GlaxoSmithKline (GSK), alleging that the company's direct-to-consumer (DTC) broadcast advertisements for the drug failed adequately to warn about the consequences of discontinuing the drug. In reviewing the new drug application for the drug, FDA had found no evidence that it was habit-forming and did not require GSK to address that risk in FDA-approved labeling. FDA did, however, require GSK to include in labeling statements regarding discontinuation syndrome, and the labeling consequently recommends that doctors gradually reduce dosages and monitor patients for syndrome symptoms. FDA reviewed proposed DTC advertisements GSK had submitted for Paxil that said that the drug was not habit-forming. The agency at no time determined that this statement was misleading. In August 2002, notwithstanding FDA's determination, the court issued a preliminary injunction prohibiting GSK from running DTC advertisements stating that Paxil is not habit-forming. (*In re Paxil Litigation,* 2002 U.S. Dist. LEXIS 16221 (C.D. Cal. Aug. 16, 2002))

On reconsideration, the court declared that the preliminary injunction challenged only "FDA's . . . determination that the public is not likely to equate the words not habit forming' as used in direct[-]to[-]consumer advertisements with no withdrawal symptoms.'" According to the court, "The question of how members of the general public are likely to interpret (or misinterpret) a statement is within one of the courts' core competencies." Declaring itself "unwilling to blindly accept FDA's ultimate determination here," the court rejected the defendants' preemption and primary jurisdiction arguments. It nevertheless denied the injunction on the ground that the plaintiff was not likely to succeed in demonstrating that "non-habit forming" statement in the advertisement is misleading. Thus, although the court ultimately declined to award the injunctive relief sought by the plaintiff, it continued to distinguish between FDA's determinations as to the adequacy of drug warnings under federal law, and its own view of warnings adequacy under state common law. (*In re Paxil Litigation,* 2002 U.S. Dist. LEXIS 24621 (C.D. Cal. Oct. 16, 2002).)

DOJ submitted to the court a Statement of Interest and a brief asserting preemption.[6] The Statement of Interest contended that a court order requiring GSK to remove the "non-habit-forming" claim from its advertisements for Paxil would be inconsistent with FDA's determination that the company's advertisements were proper and that Paxil is not, in fact, "habit-forming." The brief contended that the court should find the plaintiff's state-law request for a court order preempted because it poses an obstacle to achievement of the full objectives of Congress "by attempting to substitute th[e] Court's judgment for FDA's scientific expertise." As the brief pointed out, FDA had specifically reviewed the advertisements, made suggestions concerning the proper manner of presenting information relating to whether Paxil is "habit-forming," and, in the exercise of its scientific and medical expertise, found the advertisements acceptable. The brief also included a primary jurisdiction argument. The court reversed its earlier award of an injunction prohibiting the manufacturer from running advertisements that had been reviewed and approved by FDA, but the reversal was based on a ground other than preemption. (*In re Paxil Litigation,* 2002 U.S. Dist. LEXIS 24621 (C.D. Cal. 2002).)[7]

Conclusion

As these cases illustrate, courts entertaining lawsuits filed under state law do not always defer to FDA on matters that Congress has placed squarely within the agency's authority. In FDA regulatory areas characterized by comprehensive regulation and requiring a careful and expert evaluation of scientific data and public health issues, state coregulation can stand as an obstacle to or directly conflict with the agency's administration of its statutory mandate. Preemption is the constitutionally prescribed mechanism for resolving these conflicts.

The practice of citing preemption and primary jurisdiction under the FDCA in litigation in which the United States is not a party is well-established and substantially predates the current Administration. DOJ and FDA participation in these cases is unusual. In the current Administration, DOJ has participated in private state-law actions on FDA's behalf only following a judicial finding that the action should proceed, and only to address a state-law finding that, left undisturbed, would

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[6] Statement of Interest of the United States of America, *In re PAXIL Litigation,* Case No. CV 01–07937 MRP (CWx) (C.D. Cal. filed August 20, 2002); Brief of the United States of America, *In re PAXIL Litigation,* Case No. CV 01–07937 MRP (CWx) (C.D. Cal. filed Sept. 4, 2002).

[7] In December 2003 (296 F. Supp. 2d 1374), the litigation, consisting of twelve action in eleven federal judicial districts, was centralized for pretrial proceedings in the United States District Court for the Central District of California.

undermine FDA's execution of its statutory mission or directly conflict with federal law. Responsibility for making final decisions whether to make submissions in private lawsuits, on preemption, primary jurisdiction, or any other issue, rests with the Department of Justice—not FDA itself.

Question. These arguments conflict with long-standing FDA policy. The law appears to contradict what the FDA has argued. What motivated FDA to change its policy?

Answer. The Government's participation in cases arising under state-law and presenting preemption issues is consistent with past FDA practice and with the pertinent law.

The principal enabling statute of the Food and Drug Administration is the Federal Food, Drug, and Cosmetic Act, FDCA. Under this statute, FDA has broad authority to protect the public health by ensuring that foods are safe, wholesome, sanitary, and properly labeled, and that drugs and medical products are safe and effective. (See 21 U.S.C. § 393(b)(2)(A)–(C).) By operation of the Supremacy Clause of the United States Constitution (U.S. Const. Art. VI, clause 2), the FDCA nullifies conflicting requirements established by the States in legislation, regulations, or common law. (See *Gibbons* v. *Ogden,* 22 U.S. (9 Wheat.) 1, 211 (1824) (Marshall, C.J.).)

In the past, FDA has addressed conflicting state requirements in the context of rulemaking. In 1982, for example, FDA promulgated regulations requiring tamper-resistant packaging for over-the-counter drugs. In the preamble accompanying the regulations, FDA stated its intention that the regulations preempt any state or local requirements that were "not identical to . . . [the rule] in all respects." (47 FR 50442, 50447; Nov. 5, 1982.) Similarly, in 1986, FDA issued regulations requiring aspirin manufacturers to include in labeling a warning against use in treating chicken pox or flu symptoms in children due to the risk of Reye's Syndrome. In the accompanying preamble, FDA said the regulations preempted "State and local packaging requirements that are not identical to it with respect to OTC aspirin-containing products for human use." (51 FR 8180, 8181; Mar. 7, 1986.) In 1994, FDA amended 21 CFR 20.63 to preempt state requirements for the disclosure of adverse event-related information treated as confidential under FDA regulations. (59 FR 3944; Jan. 27, 1994.)

In addition, for many years, conflicting state requirements have been addressed by FDA through case-by-case participation in selected lawsuits to which the United States has not been a party. Because FDA lacks independent litigating authority, this participation has been by the Department of Justice (DOJ) on FDA's behalf. The practice of addressing conflicting state requirements through participation in litigation dates back many years. For example, DOJ participated on FDA's behalf in favor of preemption in both *Jones* v. *Rath Packing Company,* 430 U.S. 519 (1977), and *Grocery Manufacturers of America, Inc.* v. *Gerace,* 755 F.2d 993 (2d Cir. 1985). In addition, as discussed in our response to the previous question on preemption, FDA has recently participated in several cases involving state-law requirements for the communication of risk information for prescription drugs. Of note, the first—and most aggressive, from a legal perspective—of these submissions occurred during the previous Administration—Bernhardt case included in materials for the record.

NARMS

Question. What is the total amount of funding for NARMS, and from what account does it come?

Answer. The total amount of funding for NARMS in fiscal year 2004 is $7.634 million. This funding is located in the Salaries and Expenses, or S&E, account.

Question. How much is FDA giving to USDA and CDC in fiscal year 2005? How does that compare to fiscal year 2004? Please describe what factors are used to determine the division of funds.

Answer. At this time, FDA has not determined the exact funding for CDC and USDA for NARMS for fiscal year 2005 but plans to make decisions by Fall 2004. In fiscal year 2004, FDA funding on NARMS will be reduced due to government-wide rescissions. In fiscal year 2004, FDA provided funds of approximately $1.6 million to USDA and $2 million to CDC. It is important to point out that a large portion of the funds provided to CDC is given to the states for the collection, isolation and identification of bacterial isolates, which are then shipped to CDC and the Food and Drug Administration's Center for Veterinary Medicine—NARMS retail arm—for susceptibility testing. In determining the funds provided to CDC and USDA, we analyze the entire NARMS program, including the retail food arm of NARMS, and strive to fill in data gaps and avoid duplication of organisms to be tested.

Question. How much NARMS money is currently being spent in foreign countries, specifically Mexico? How is this money being used?

Answer. FDA is not spending any current year NARMS funding in Mexico or other foreign countries.

Question. Does USDA or CDC spend any of their NARMS money in foreign countries?

Answer. In fiscal year 2004 FDA is providing USDA and CDC, $1.6 million and $2 million respectively. FDA does not keep detailed records of USDA and CDC funding for NARMS.

COUNTERFEIT DRUGS

Question. In February, FDA released a report on combating counterfeit drugs. Several new technologies were mentioned that could be used to this effect, including Radiofrequency Identification tagging, color shifting inks, and holograms. Specifically regarding color shifting inks, which I understand are currently available, has FDA taken any action, or do you have any plans to pursue this option?

Answer. It is true that color shifting ink technology is currently available for use on drug packaging and labeling. However, we heard uniformly from all stakeholders that this technology is expensive and requires significant investment of resources and time prior to implementation. Due to the wide variety of products, packaging, and labeling on the market, we heard from manufacturers, wholesalers, and retailers that the decision to use color shifting inks, or any other authentication technology, should be made by the manufacturer after a manufacturer initiated product risk assessment. Without such an analysis, use of color-shifting ink, or other authentication technology, could lead to an unnecessary increase in the cost of drugs to consumers. For example, we heard that color-shifting ink could be appropriate for use on a very expensive, high volume brand name drug product that is likely to be counterfeited, but not on a generic or low volume drug product that is less likely to be counterfeited.

Based on our discussions with manufacturers, we estimate that it would take a minimum of six to twelve months to implement a technology such as color shifting ink from the time a decision is made to use the authentication technology on the packaging and/or labeling of a drug product. It could take longer if the technology, e.g., color-shifting ink, is used on the product itself because safety studies might have to be performed to ensure that the technology, e.g., the ink, does not affect the safety or stability of the product.

ANIMAL DRUG COMPOUNDING

Question. Dr. Crawford, on February 10, I submitted a letter to Dr. McClellan regarding FDA's new Compliance Policy Guidelines, issued July 14, 2003, regarding animal drug compounding. I received a response from FDA on March 31st, and I thank you for that. However, I do have a few more questions in light of the response.

First, the letter stated that FDA issued the CPG for immediate implementation because of the "urgent need to explain how it intended to exercise its enforcement discretion regarding compounded drugs for animal use in light of *Thompson* v. *Western States Medical Center*." However, this case dealt only with compounding in human drugs, not animal drugs. How does this create an urgent need to deal with animal drugs?

Answer. After the *Western States* decision, FDA revised its enforcement policy on pharmacy compounding of human drugs. FDA was concerned that without updated guidance regarding compounding of animal drugs, the public would remain uncertain about whether and how FDA would change its enforcement policy with respect to compounded animal drugs. In addition, agency staff would lack clear guidance on enforcement matters.

As FDA stated in its letter, although prior public comment was not sought in this case, pursuant to the good guidance practices regulations the public was invited to comment on the CPG when it was issued and may comment on it at any time (68 FR 41591 (July 14, 2003)). FDA has been reviewing those comments and will revise the guidance as appropriate upon completion of our review.

Question. Second, the response states that two federal appeals court decisions have held that "the Federal Drug & Cosmetic Act does not permit veterinarians to compound unapproved finished drugs from bulk substances, unless the finished drug is not a new animal drug. These cases support FDA's position that new animal drugs that are compounded from bulk substances are adulterated under the FD&C Act and may be subject to regulatory action." I have been informed that the cases cited deal only with veterinarians compounding drugs, not pharmacists. Why do you limit pharmacists as well as veterinarians? Is this supported by any congressionally-enacted statutory authority, legislative history or case law?

Answer. The principle established by the courts applies equally to compounding by pharmacists and veterinarians.

Veterinary medicine has not traditionally utilized the services of compounding pharmacies to the extent that they have been utilized within human medicine. The increasing activities and presence of compounding pharmacies in veterinary medicine is a relatively recent development.

The Federal Food Drug and Cosmetic Act, or "the Act", and its implementing regulations do not exempt veterinarians or pharmacists from the approval requirements in the new animal drug provisions of the Act, 21 U.S.C. Section 360b. In the absence of an approved new animal drug application, the compounding of a new animal drug from any unapproved drug or from bulk drug substances results in an adulterated new animal drug within the meaning of section 21 U.S.C. Section 351(a)(5). The compounding of a new animal drug from an approved human or animal drug also results in an adulterated new animal drug within the meaning of 21 U.S.C. Section 351(a)(5), unless the conditions set forth in 21 CFR 530.13(b) relating to extralable use are met.

FDA is concerned about veterinarians and pharmacists that are engaged in manufacturing and distributing unapproved new animal drugs in a manner that is clearly outside the bounds of traditional pharmacy practice and that violates the Act—such as compounding that is intended to circumvent the drug approval process and provide for the mass marketing of products that have been produced with little or no quality control or manufacturing standards to ensure the purity, potency, and stability of the product.

Pharmacists and veterinarians who engage in activities analogous to manufacturing and distributing drugs for use in animals may be held to the same provisions of the Act as manufacturers.

Question. Finally, the final paragraph of the FDA response states "Accordingly, the regulations that implement AMDUCA provide that extralabel use by compounding applies only to compounding of a product from approved drugs, and that nothing in the regulations is to be construed as permitting compounding from bulk drugs." Is there in the agency's view anything in AMDUCA's regulations or the Act that is to be construed as not permitting compounding from bulk substances?

Answer. As previously noted, under the Federal Food, Drug and Cosmetic Act, in the absence of an approved new animal drug application, the compounding of a new animal drug from a bulk substance results in a new animal drug that is adulterated as a matter of law. This has been FDA's longstanding position, which is supported by two federal appeals court decisions, *United States* v. *Algon Chemical Inc.*, 879 F.2d 1154 (3d Cir. 1989) and *United States* v. *9/1 Kg. Containers,* 854 F.2d 173 (7th Cir. 1988).

CONCLUSION OF HEARINGS

Senator SPECTER. Thank you all very much for being here. That concludes our hearings.

[Whereupon, at 10:48 a.m., Thursday, April 1, the hearings were concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]