DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 2003

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

HOUSE OF REPRESENTATIVES

ONE HUNDRED SEVENTH CONGRESS

SECOND SESSION

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

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

CRAIG HIGGINS, SUSAN QUANTIUS, SUSAN ROSS FIRTH, MEG SNYDER, and FRANCINE MACK-SALVADOR, *Subcommittee Staff*

PART 4A

NATIONAL INSTITUTES OF HEALTH

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PART 4A

NATIONAL INSTITUTES OF HEALTH



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NATIONAL INSTITUTES OF HEALTH BUDGET OVERVIEW

Panel: From Bench to Bedside and Beyond
NIDDK, NCI, NIA, NINDS, and NIAID

Panel: Biomedical Science in the Future
NIBMS, NIDCD, CSR, NIMH, NIDA, NCRR and B&F

Panel: Collaborations in Research
NIAMS, NICHD, NIBIB, FIC, NCMHD, NCCAM

Panel: Disease Prevention and Health Promotion
NINR, NLM, NIEHS, NEI, NIDCR, NHLBI, NHGRI and NIAAA

DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION AND RELATED AGENCIES APPROPRIATIONS FOR 2003

WEDNESDAY, MAY 1, 2002.

EFFORTS TO PREPARE AGAINST BIOTERRORISM

WITNESSES

CLAUDE ALLEN, DEPUTY SECRETARY
ELIZABETH JAMES DUKE, ADMINISTRATOR, HEALTH RESOURCES AND SERVICES ADMINISTRATION
DAVID W. FLEMING, ACTING DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION
ANTHONY FAUCI, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
CHARLES CURIE, ADMINISTRATOR, SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION

CHAIRMAN'S STATEMENT

Mr. REGULA. We'll get started this morning. We have an interesting morning and a very important panel to present the story of bioterrorism as it relates to the Federal Government.

Mr. Allen, I understand that you're in charge, you'll kick it off then you'll call on your colleagues to give their reports, then we'll go to questions. So your statement will be made part of the record. We'll appreciate a summarization.

DEPUTY SECRETARY'S STATEMENT

Deputy Secretary ALLEN. Thank you, Mr. Chairman, members of the Committee. Thank you for inviting the Department of Health and Human Services here today to discuss the President's fiscal year 2003 request for our bioterrorism preparedness efforts.

I do want to take a moment and stress to you that being ready for a bioterrorist event is an important part of our homeland security. I want to thank each of you for being so supportive of the President and Secretary Thompson's efforts to build and enhance the necessary protections to ensure the safety and the public health of our Nation.

I have several of our agency heads here with me today, and I would like to take a moment to introduce them to you. At my right, your left, is Dr. Elizabeth James Duke, Betty Duke as we affectionately refer to her, who is our Administrator for the Health Resources and Services Administration. Dr. David Fleming is the Act-

ing Director for the Centers for Disease Control and Prevention. Dr. Tony Fauci is the Director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. And Mr. Charles Curie is the Administrator for the Substance Abuse and Mental Health Services Administration.

We're proposing a comprehensive and aggressive approach to improving our public health infrastructure to combat bioterrorism and other public health threats we may face. The fiscal year 2003 bioterrorism budget request for HHS is $4.3 billion, which is an increase of $1.3 billion, or 45 percent over fiscal year 2002. Of this amount, $2.3 billion is requested in the public health and social services emergency fund $1.75 billion in the National Institutes of Health, and another $120 million in the health facilities construction and management fund for the Centers for Disease Control and Prevention facilities. And lastly, $159 million in the Food and Drug Administration.

Our State and local public health preparedness system is our first line of defense against bioterrorism. In order to create a blanket of protection, the fiscal year 2003 budget provides $918 million in funding to State and local health departments to improve laboratory capacity, enhance epidemiological expertise in the identification and control of diseases caused by bioterrorism, and provide for better electronic communications and distance learning.

This is in addition to the $1.1 billion provided this year for State and local health departments and their partners to equip and train themselves to respond to potential acts of bioterrorism and other public health threats and emergencies stemming from a terrorist attack. We want to make sure that State and local health departments are fully staffed and trained, have strengthened lab capacity and increased lab capacity, and have secure information systems and solid communication capabilities. These are some of the areas we'll be focusing on. You'll hear more about our health alert network, Dr. Fleming oversees that at the Centers for Disease Control. I'll let him speak to you about that as well.

In addition, we'll talk about CDC, we'll also enhance their communication backbone for the next generation disease surveillance via the National Electronic Disease Surveillance System, which you can hear more about as well. These systems will assist but never replace the interaction of alert clinicians and well trained public health epidemiological response and outbreak control staff. We saw how the interaction and their interaction worked in Florida in identifying the first case of inhalational anthrax.

We also know that our medical system must work hand in glove with the public health system in both the detection of bioterrorist attacks and in the treatment of its victims. So we're working closely with the States to ensure integration of our efforts at all levels, and they have been asked to develop their public health and hospital preparedness plans in tandem.

A key ingredient of our strategy is ensuring that the Nation's hospitals are well prepared. A total of $518 million is requested for two programs. HRSA is responsible for leading this aspect of preparedness, and the agency will continue the hospital preparedness program begun in fiscal year 2002.

Two hundred thirty-five million dollars, an increase of $100 million, is requested to continue cooperative agreements with health departments and States and other eligible entities to care for victims of bioterrorism by upgrading the capacity of hospitals, outpatient facilities, emergency medical service systems and poison control centers.

Additionally, to address hospital infrastructure, development for laboratories, HRSA will use $283 million to ensure adequate hospital laboratory capacity to diagnose and report on potential biological and chemical agents that might be used by terrorists. They will also work to help hospitals improve their capabilities to control infections and assist hospitals with the purchase of personal protective equipment, which is so vitally important to them in providing first responder services. We will also focus on infectious disease containment systems, as well as other equipment for decontamination of biological and chemical agents.

We also will be expanding the number of Epidemic Intelligence Service officers by providing a Federal epidemiologist officer in every State, complete the 25 new metropolitan medical response systems begun in fiscal year 2002. We will also be reaching the planned total of 122 total MMRS systems around the country. And further, fund the readiness of our disaster medical assistance teams and the National Disaster Medical System assets.

In addition, we can talk further about the additional investments in the national pharmaceutical stockpile. The Department's goal is to maintain a sufficient quantity of antibiotics to care for 20 million individuals exposed to anthrax, to procure up to 25 million doses of the next generation anthrax vaccine currently under development, and to have sufficient stockpiles of smallpox vaccine and treatment for vaccine side effects, what we call VIG, to immunize the entire population in the event of an attack, and rapid deployment at the Federal, State and local level to distribute the national pharmaceutical stockpile assets if deployed.

I want to thank you again for the support of this Committee and your colleagues, Mr. Chairman, here in Congress, that you've provided in passing the fiscal year 2002 appropriation. There has been tremendous progress made. The day the appropriation was signed into law, we bought 100 million doses of Ciprofloxacin, you've given us the funding we need to order enough quantities of smallpox vaccine to protect every American.

And with the recent donation of some 1950s smallpox vaccine by Aventis Pasteur, we can respond in an emergency even sooner than anticipated. We have also given States the first round of grants to prepare themselves to be able to use these resources in an emergency.

Even with these advances that we've made, and this progress, we still have more work to do. Our budget includes $650 million for procurement of vaccines and pharmaceuticals, stockpile management and related preparedness activities. Again, I will talk finally about the National Institutes of Health and what's going on there.

Our bioterrorism request for NIH is $1.75 billion, which is over a six-fold increase for NIH's bioterrorism spending over fiscal year 2002. It represents approximately 40 percent of the total NIH increase for 2003.

NIH's bioterrorism research plan calls for expanded basic research on the physiology and genetics of potential bioterrorist agents, accelerated discovery, development and clinical research of next generation vaccines, therapies and diagnostic tests, and expanded research infrastructure at both the intramural and extramural levels in order to be able to conduct this research in safe and up to date facilities.

In particular, the advancement of knowledge should have enormous positive impacts on our ability to diagnose, treat and prevent major killer diseases, such as malaria, tuberculosis, HIV–AIDS, and a spectrum of emerging and re-emerging diseases, such as West Nile fever, dengue, influenza, and multi-drug resistant microbes.

We have to make sure that the Nation's mental health is also in order, and at the Secretary's request last November, SAMHSA convened a national summit to bring focus to the mental health problems arising from the bioterrorism or other traumatic events. The fiscal year 2003 budget includes $10 million to assist State and local organizations in developing solutions and plans to meet the mental health needs that arise from bioterrorist incidents.

Finally, the Department's request of $159 million for the Food and Drug Administration reflects the President's commitment to promote and protect the public health by assuring that safe and effective products reach the market in a timely way and to monitor products for continued safety after they are in use. I realize this request comes before the Agricultural, Rural Development, Food and Drug Administration and Related Agencies Subcommittee, but it is an important element in our defense against bioterrorism.

As you see, we have made substantial progress to date in enhancing the Nation's capability to respond to biological or chemical attacks, or terrorism. I thank you for the resources you have made available this year, and look forward to working with you to further strengthen our defenses against bioterrorism.

Mr. Chairman, that concludes my remarks, and I would now like for our other witnesses to present brief testimony on their specific agency's activities. Then we would be pleased to answer any questions you or the Committee members may have.

[The information follows:]

HHS EFFORTS TO PREPARE AGAINST BIOTERRORISM
ORAL TESTIMONY FOR THE HONORABLE CLAUDE A. ALLEN
BEFORE THE HOUSE SUBCOMMITTEE ON LABOR-HHS-EDUCATION APPROPRIATIONS
MAY 1, 2002
10:15 A.M.

Good morning, Chairman Regula, Mr. Obey, and Members of the Committee, thank you for inviting the Department of Health and Human Services (HHS) here today to discuss the President's FY 2003 request for our bioterrorism preparedness efforts.

Being ready for a bioterrorist event is an important part of our homeland security, and I want to thank each of you for being so supportive of the President and Secretary Thompson's efforts to build and enhance the necessary protections to ensure the safety and public health of our nation.

I have several of our agency heads with me to provide you with more details about their specific areas within the Department, and I would like to introduce them at this time.

Dr. Betty James Duke is the Administrator of the Health Resources and Services Administration (HRSA). Charles Curie is the Administrator of the Substance Abuse and Mental Health Services Administration. Dr. David Fleming is the Acting Director of the Centers for Disease Control and Prevention (CDC). And Dr. Tony Fauci is the Director of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH).

We are proposing a comprehensive and aggressive approach to improving our public health infrastructure to combat bioterrorism and other public health threats we may face.

The FY 2003 bioterrorism budget request for HHS is $4.3 billion, which is an increase of $1.3 billion, or 45 percent, above FY 2002. Of this amount, $2.3 billion is requested in the Public Health and Social Services Emergency Fund, $1.75 billion in the National Institutes for Health, $120 million in the Health Facilities Construction and Management Fund for the Centers for Disease Control and Prevention facilities, and $159 million in the Food and Drug Administration.

Our state and local public health system is our first line of defense against bioterrorism. In order to create a blanket of protection, the FY 2003 budget provides $918 million in funding to state and local health departments to improve laboratory capacity, enhance epidemiological expertise in the identification and control of diseases caused by bioterrorism, and provide for better electronic communication and distance learning.

This is in addition to the $1.1 billion provided this year for state and local health departments and their partners to equip and train themselves to respond to potential acts of bioterrorism and other public health threats and emergencies stemming from a terrorist attack.

We want to make sure that state and local health departments are fully staffed and trained, have strengthened lab capacity and increased lab capacity, have secure information systems, and solid communication capabilities.

Crisis communications is one of the key areas we will be addressing. The CDC is making a significant investment in building the nation's public health communications infrastructure and is enhancing the Health Alert Network (HAN). HAN is a nationwide program designed to establish internet communications via connectivity with public health departments in at least ninety percent of our nations' counties.

The CDC will also enhance the communication backbone for next-generation disease surveillance, via the National Electronic Disease Surveillance System (NEDSS).

These systems will assist, but never replace, the interaction of alert clinicians and well-trained public health epidemiological response and outbreak control staff. We saw how that interaction worked in Florida in identifying the first case of inhalational anthrax.

We know that our medical system must work hand in glove with the public health system in both the detection of bioterrorist attacks and the treatment of its victims. We are working closely with the states to ensure integration of our efforts at all levels, and they have been asked to develop their public health and hospital preparedness plans in tandem.

A key ingredient is assuring that the nation's hospitals are well prepared. A total of $518 million is requested for two programs. HRSA is responsible for leading this aspect of preparedness, and the agency will continue the Hospital Preparedness program begun in FY 2002.

$235 million, an increase of $100 million, is requested to continue cooperative agreements with health departments in states and other eligible entities to care for victims of bioterrorism by upgrading the capacity of hospitals, outpatient facilities, emergency medical services systems, and poison control centers.

To address hospital infrastructure development for laboratories, infection control, and decontamination issues, HRSA will use $283 million to ensure adequate hospital laboratory capacity to diagnose and report on potential biological and chemical agents that might be used by terrorists, help hospitals improve their capabilities to control infection, and assist hospitals with the purchase of personal protective equipment, infectious disease containment systems, and other equipment for decontamination of biological and chemical agents.

We will expand the number of Epidemic Intelligence Service officers by providing a Federal Epidemiologist officer in every state, complete the 25 new Metropolitan Medical Response Systems (MMRS) begun in FY 2002, reaching the planned total of 122, and further fund the readiness of the Disaster Medical Assistance Teams and National Disaster Medical Systems assets.

An important part of the war against terrorism is having a ready supply of essential vaccines and a robust National Pharmaceutical Stockpile. If a bioterrorist attack occurs, our state and local public health workers and hospitals must have access to adequate medicines.

The Department's goals are to maintaining a sufficient quantity of antibiotics to care for 20 million individuals exposed to anthrax, procure up to 25 million doses of a next-generation anthrax vaccine currently under development, have sufficient stockpiles of smallpox vaccine and treatment for vaccine side effects to immunize the entire population in the event of an attack, and rapid deployment at the federal, state, and local level to distribute National Pharmaceutical Stockpile assets if deployed.

Thanks to the support you and your colleagues in Congress provided in passing the FY 2002 appropriation, tremendous progress has been made. The day that appropriation was signed into law, we bought 100 million doses of Cipro.

You have given us the funding we need to order enough quality smallpox vaccine to protect all Americans. With the recent donation of some 1950's smallpox vaccine by Aventis, we can respond in an emergency even sooner than anticipated. We have also given States the first round of grants to prepare themselves to be able to use these resources in an emergency.

Even with this progress, we still have more work to do. Our Budget includes $650 million for procurement of vaccines and pharmaceuticals, stockpile management, and related preparedness activities.

While we stockpile the pharmaceuticals and vaccines that are available today, we must also make major investments in the development of new drugs, vaccines, and diagnostic procedures.

Our bioterrorism request for the National Institutes of Health is $1.75 billion, which is over a six-fold increase above NIH's bioterrorism spending in FY 2002 and represents approximately 40 percent of the total NIH increase for FY 2003.

NIH's bioterrorism research plan calls for expanded basic research on the physiology and genetics of potential bioterrorism agents, accelerated discovery, development, and clinical research of next generation vaccines, therapies, and diagnostic tests, and expanded research infrastructure at both the intramural and extramural levels in order to be able to conduct this research in safe and up-to-date facilities.

In particular, the advancement of knowledge should have enormous positive impact on our ability to diagnose, treat, and prevent major killer-diseases such as malaria, tuberculosis, HIV/AIDS, and a spectrum of emerging and re-emerging diseases such as West Nile fever, dengue, influenza, and multi-drug resistant microbes.

We have to make sure that the nation's mental health is in order. At the Secretary's request, last November SAMHSA convened a national summit to bring focus to the mental health problems arising from a bioterrorism or other traumatic events.

The FY 2003 budget includes $10 million to assist State and local organizations in developing solutions and plans to meet the mental health needs that arise from a bioterrorist incident.

Finally, the Department's request of $159 million for the Food and Drug Administration reflects the President's commitment to promote and protect the public health by ensuring that safe and effective products reach the market in a timely way and to monitor products for continued safety after they are in use. I realize this request comes before the Agriculture, Rural Development, Food and Drug Subcommittee, but it is an important element in our defense against bioterrorism, and I wanted to mention it to you.

As you can see, we have made substantial progress to date in enhancing the nation's capability to respond to biological or chemical acts of terrorism. I thank you for the resources you made available this year and look forward to working with you to further strengthen our defenses against bioterrorism.

Mr. Chairman, that concludes my remarks. I would now like for our other witnesses to present brief testimony on their specific agency's activities, and then we would be pleased to answer any questions you or members of the Committee may have.

Deputy Secretary ALLEN. We'll start with Dr. Fauci.

DIRECTOR OF NIAID STATEMENT

Dr. FAUCI. Thank you, Mr. Chairman. It's a pleasure to be here again before the Committee, members of the Committee.

I'm going to spend just a couple of minutes outlining for you the NIH's plan, strategic plan and research agenda, as it were, for the biodefense effort at the NIH. This first poster really addresses the underlying strategy and philosophy of the entire department, vis-a-vis biodefense. And it's titled Biowarfare versus Bioterrorism. Because it really underscores the important difference, although there are overlaps between what we do and what the Department of Defense does, in multiple agencies within the Department of Health and Human Services.

First of all, the population that we need to protect is much more diverse with regard to age and health than the military population. We're responsible for infants, children, elderly, pregnant women, individuals who are on medications and individuals with immunosuppressive diseases. Therefore, the scope of what we need to deal with with regard to therapies and vaccines is highly complicated and certainly much more difficult.

Also, the military plans would emphasize one strategy, namely vaccines. As you will hear, probably in the question period, we have vaccines as an important component of our armamentarium, but we also need the diagnostics and therapeutics.

Finally, the agents that we need to deal with are much greater in number. Because although the attacks on the military would emphasize highly efficient killers, in the civilian population, any microbe that's unleased upon us that would cause a significant amount of terror, even if the biological impact is minimum, we've already experienced that with the anthrax situation here in Washington and in other cities in our country.

So if I could have the next slide, Deputy Secretary Allen mentioned to you the budget request for the NIH within the scope of the Department. It's approximately $1.75 billion. The breakdown of that is illustrated here on this slide. As you can see, there is a significant amount on basic biomedical research into the physiology of the microbes as well as the host defense mechanisms, which as I'll get to in just a moment, are relevant for the other diseases that Deputy Secretary Allen mentioned, namely other emerging diseases. There will be a significant amount on research facilities, because unlike the war on cancer and the war on HIV–AIDS, there are certain facilities that are necessary to not only protect the researchers, but also the communities surrounding the research facilities.

We have already, in anticipation of the defense of this budget, put together a comprehensive strategic plan for biodefense as well as a research agenda for the high priority agents, which we refer to as Category A agents, including smallpox, anthrax, Ebola, botulism, tularemia and others. In that regard, the plan that we are dealing with now and will project for the next several years is anchored in basic research with appropriate facilities, but also for that amount of money, would have to deliver to the American peo-

ple definable milestones and end points in the form of vaccines, diagnostics and therapeutics.

In that regard, I'm happy to report that with the supplement that we generously received from the Congress in 2002, together with the plans for what we'll do in 2003, we have already made some significant accomplishments, some of which I've already mentioned to this Committee in the main NIH hearing. They have to do with the highly successful smallpox vaccination dilutional study that has now brought us already immediately to approximately 77 million doses. You already heard from Deputy Secretary Allen about the purchases and the Aventis Pasteur 1950's vaccine, which will again bring us to the point where we will have enough vaccine, if necessary, to vaccinate everyone in the country.

There's also the important anthrax pathogenesis advances that have been made, together with the efforts that we have right now, of moving rapidly into a phase one clinical trial on the second generation of the anthrax. Finally, I'm happy to report that even in Ebola, we now have shown in an animal model that we can protect monkeys from challenge with Ebola vaccine, and we will be entering phase one clinical trials in humans before the end of this calendar year.

Finally, as this headline from News Day shows, the worst bioterrorist may be nature itself. That refers to the comment just a moment ago by Deputy Secretary Allen about emerging and re-emerging diseases. Because in the Department, we look upon deliberate release of microbes in a bioterrorist event to be obviously important and something we need to address, and we are addressing that.

But that really is part of the broader picture and the responsibility of the Department of addressing emerging and re-emerging diseases, as shown on this final poster, where we had the flu pandemic, which really was truly a bioterror agent. Not deliberately, but naturally evolving, that killed 25 million people in 1918, 750,000 in the United States. The AIDS epidemic, you've heard from me many times before this Committee, 40 million people living with HIV, 23 million already dead.

The bioterrorism events that we have faced and likely will face again is really part of that emerging and re-emerging disease phenomenon. Because of that, we are building a sustainable effort that will serve us well not only for the immediate threats of deliberately released microbes, but for the decades ahead of what we'll have to face in emerging and re-emerging diseases from natural causes.

Thank you very much, Mr. Chairman.

[The information follows:]

Biowarfare versus Bioterrorism

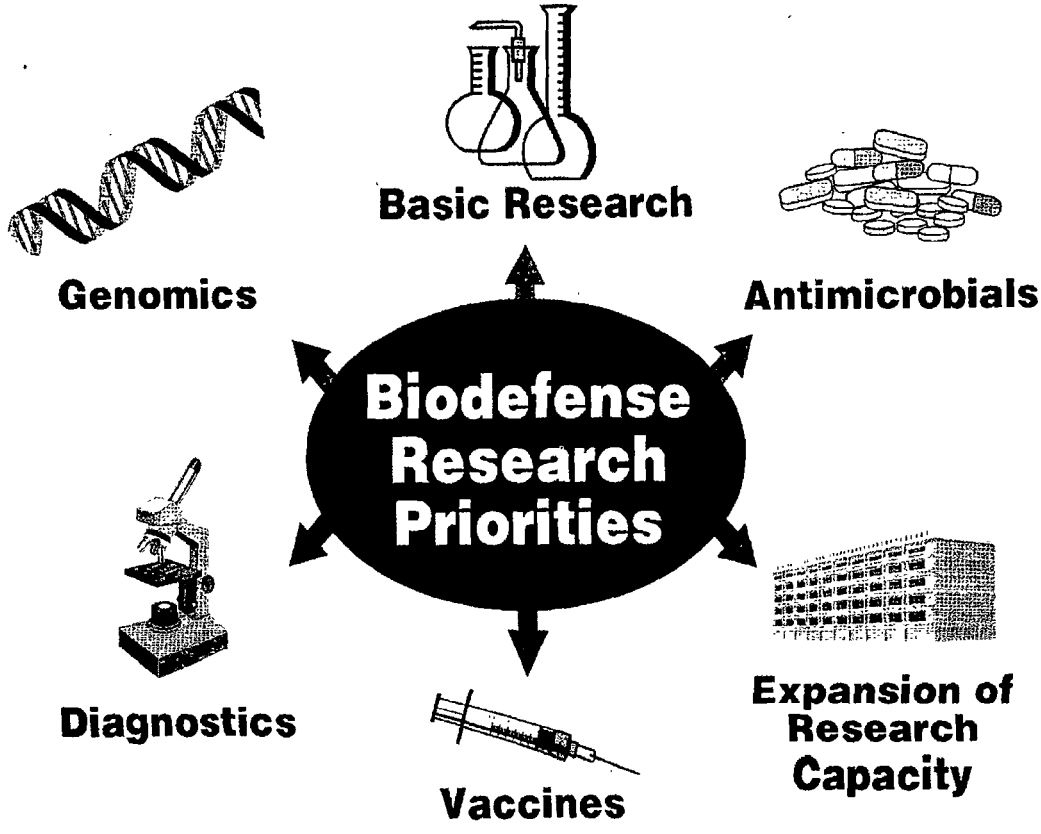
- The civilian population is significantly more diverse than the military with regard to age and health.
- Military plans for attacks emphasize vaccine prevention. Civilian attacks will be sudden and unexpected, requiring rapid diagnostics and antimicrobial treatments.
- Potential agents of bioterrorism in civilian settings are more numerous than potential military biological weapons.

NIH Biodefense Research Funding, FY 2003 (President's Budget)

Basic Research and Development	$440.6M
Drug/Vaccine Discovery and Development	$591.9M
Clinical Research	$194.3M
Research Facilities Construction*	$521.1M
	$1,747.9M

*Research Facilities in FY 2003: $150M extramural, $371M intramural

NIAID Strategic Plan for Biodefense Research
February 2002
Responding
through
Research
NIAID Biodefense Research Agenda for CDC Category A Agents
February 2002
Responding
through
Research


Basic Research
Genomics
Antimicrobials
Biodefense Research Priorities
Diagnostics
Expansion of Research Capacity
Vaccines

Recent NIH Biodefense Research Accomplishments

Smallpox

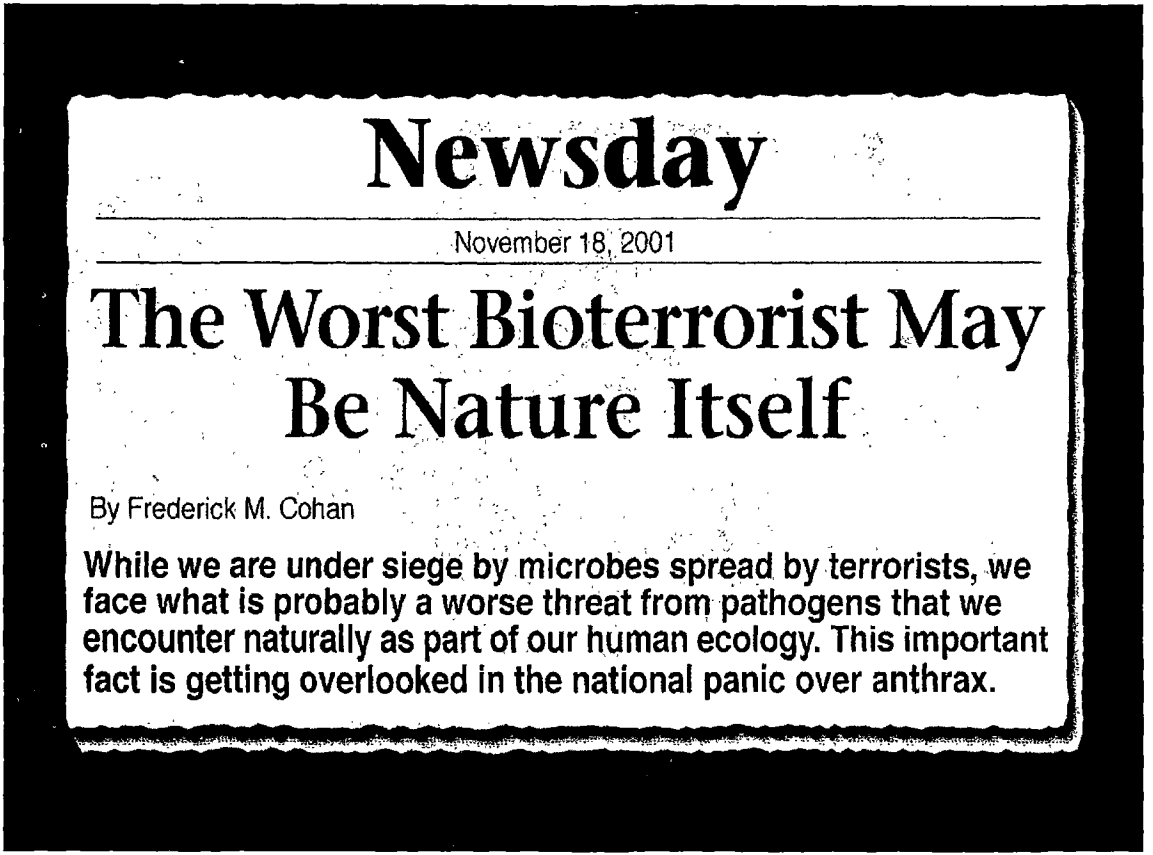
- Vaccine dilution studies
- Vaccine development
- Antiviral drug development

Anthrax

- Pathogenesis
- Genomic sequencing
- Vaccine development

Ebola

- Pathogenesis
- Vaccine development



Newsday

November 18, 2001

The Worst Bioterrorist May Be Nature Itself

By Frederick M. Cohan

While we are under siege by microbes spread by terrorists, we face what is probably a worse threat from pathogens that we encounter naturally as part of our human ecology. This important fact is getting overlooked in the national panic over anthrax.

Emerging Infectious Diseases: A Continuing Threat



ADMINISTRATOR OF SAMHSA STATEMENT

Mr. CURIE. Mr. Chairman, I'm Charles Curie, the Administrator of SAMHSA. First, let me thank the members of the Subcommittee for calling this important hearing. It's a privilege for me to sit before you with Deputy Secretary Claude Allen and my colleagues to discuss the Department's efforts to respond to threats of and actual acts of bioterrorism.

As the Nation's lead voice for mental health and substance abuse, SAMHSA recognizes that we all have an unprecedented opportunity to face a challenge of the future. Being that any act of bioterrorism will inevitably create enormous mental health and other behavioral health consequences, we need to recognize that planning for and responding to acts of bioterrorism is different from anything we have known. This is simply uncharted territory.

The fields of mental health and substance abuse are simply not prepared in terms of an adequate response and treatment capacity, evidence based intervention nor a properly trained work force. Immediately after I was confirmed as SAMHSA administrator, Secretary Thompson, as Deputy Secretary Allen indicated, asked me to convene a meeting with State representatives to focus on the mental health and substance abuse impacts of terrorism and bioterrorism. In November, Governors from 45 States and jurisdictions sent teams representing not only mental health and substance abuse authorities, but Departments of Health, Emergency Preparedness and Education, as well as local providers of mental health, substance abuse and faith-based providers and organizations, and other voluntary organizations to our national summit held in New York City.

At that summit, we had expert plenary sessions in which we brought in the best thinkers in the country as we were actually creating the field of dealing with the mental health and substance abuse consequences of bioterrorism. The good news is that there had been work done in the previous years out of the Center for Mental Health Services in SAMHSA, under the leadership of Brian Flynn and in consultation and collaboration with the Centers for Disease Control and prevention and our other sister operating division, to frame a mental health response. We used that information and again, some of the best thinking in the country to give information to the State teams.

We also devised a workbook, and those State teams, and there were 10 to 15 members from each State, including representatives from Governor's offices, met on their own at least three times during that three day period to begin to hammer out a plan that they could present back to their State to become part of that State's disaster response to bioterrorism. The good news is, several States indicated they could take our workbook and plug that in as a module to mental health and substance abuse. We're receiving the final draft of those plans and offering technical assistance to States at this point in time.

We asked these State teams about their needs. The Department, the Secretary, and the President responded favorably by including the $10 million that Deputy Secretary Allen indicated in the President's budget to focus on mental health and bioterrorism. This will

be the first time any Federal dollars have been designated at SAMHSA for this purpose.

In response to these stated needs, our plans for the use of these funds include technical assistance to the States, to assist them in incorporating bioterrorism readiness and response into their State emergency preparedness planning, behavioral health triage in health care settings, especially hospital emergency rooms, so that hospital personnel can devote life saving interventions to deal with those exposed to biological agents and separate out what is a psychological response to what is an actual physical danger.

Bioterrorist crisis intervention is another area, and will exist to serve people who become psychological victims of terrorist events. Then also disseminating knowledge to public officials to prepare them in averting widespread public fear and panic, overwhelming fear-induced utilization of hospital emergency rooms and other health care facilities and loss of confidence in public institutions. In other words, risk communications.

We were also able to make available at that summit a draft publication of risk communications which is being finalized now, which public officials can use to help give them guidance in dealing with the aftermath of an emergency. What public officials say in the aftermath of a bioterrorist attack or perceived attack or any disaster is probably the most important mental health intervention for the public.

There are vast unknowns when it comes to how our Nation will respond to acts of bioterrorism. We do know, however, that we have a rich history of overcoming adversity and emerging even stronger. We will be sure to continue this success by taking into account the Nation's mental health in times of terrorism. That is the only way we can truly take the terror out of terrorism.

SAMHSA also responded by sending $1 million to New York City within the first week after September 11th to help with the mental health response. An additional $6 million was sent out through the Department of Health and Human Services to the other impacted areas over the next two weeks, and within the first month a total of $28 million. Those dollars were used in conjunction with approximately $150 million that had been issued by FEMA so far for crisis counseling.

Secretary Thompson stated when he addressed the national summit, we must follow our short term responses with long term commitments. I look forward to working with you to achieve the promise of this mission. Thank you.

[The information follows:]

HHS Testimony
Before the House Subcommittee on Labor-HHS-Education Appropriations

United States House of Representatives

SAMHSA Efforts to Prepare Against Bioterrorism

Statement of
Charles G. Curie, M.A., A.C.S.W.
Administrator
Substance Abuse and Mental Health Services Administration

May 1, 2002

Center for Mental Health Services

Bioterrorism Activities and Plans

- Goal is to develop a comprehensive national approach to the mental health and substance abuse consequences of bioterrorism.

- SAMHSA has sponsored two workshops bringing together more than 40 national experts:

  - *Planning for Bioterrorism: Behavioral and Mental Health Responses to Weapons of Mass Destruction*
  - *Mass Disruption* and *Planning for Biological Events: Responses to Terrorism and Infectious Disease Outbreaks*

- In response to needs expressed by 600 State mental health and substance abuse representatives at SAMHSA's National Summit on Terrorism, SAMHSA distributed information to guide public officials in the basics of risk communication.

- FY2003 activities focus on:
  - technical assistance to States to assist them in incorporating bioterrorism readiness and response into their State emergency preparedness planning;
  - behavioral health triage in health care settings,
  - bioterror crisis intervention, and
  - disseminating knowledge to public officials to prepare them in averting widespread public fear and panic, overwhelming fear-induced utilization of hospital emergency rooms and other health care facilities and loss of confidence in public institutions.

September 11 Response and States Needs Assessment

- SAMHSA awarded $28 million in emergency supplemental funds to the 8 affected States and to the District of Columbia in direct response to September 11th.

- SAMHSA/CMHS staff continue to work closely with FEMA in monitoring Crisis Counseling Program (CCP)grants awarded after September 11th. Staff are currently working with States to develop and implement a plan of services for a 9-month grant.

- This assistance to States includes: guidance on preparing the CCP grant application, guidance on developing a plan of services appropriate to the community and the phase of the disaster, guidance on training needs and resources, and guidance on linking with other programs that can help meet mental health needs that are not covered under the CCP.

- Services supported under the initial SAMHSA Emergency Supplemental included:
  - Comprehensive assessment of long term mental health needs and infrastructure needs in order to prepare for future events
  - Hotlines
  - Crisis response training to mental health providers
  - Media campaigns to educate the community about mental health responses to terrorism and where to seek help

- Services requested in the comprehensive needs assessment include:
  - Increase direct service capacity (increase in facilities, staff, equipment, etc)
  - Increase capacity to provide temporary crisis interventions, including the development of mental health response teams
  - Create an office of behavioral health disaster preparedness and response and establish a disaster mental/behavioral health response coordinator
  - Improve preparedness and planning activities through cross-agency activities
  - Increase training capacity, especially for trauma interventions and traumatic bereavement interventions

- SAMHSAs Center for Substance Abuse Treatment is developing two methods of information dissemination in direct response to terrorism:
  - A new Treatment Improvement Protocol (TIP) is being planned on the effects of trauma and disaster on substance abuse, and
  - A newsletter focusing on Post Traumatic Stress Disorder (PTSD) and substance abuse.

- Since 9/11, CSAP prevention resources have been used to implement state and local substance abuse prevention strategies.
  - Schools and communities have marshaled prevention efforts both during and after school hours to help affected children & families.
  - "Preventionists" have implemented peer leader trainings for youth, as well as, family substance abuse prevention provider training presentations designed to enhance the capacity for incorporating substance abuse prevention strategies with those that address post traumatic stress issues for children and families.
  - Funding has also supported workplace services (EAP).

- Building statewide substance abuse prevention capacity to plan for any future terrorism/bio-terrorism is critical. Our goal is to work closely with state substance abuse prevention agencies and local service provider systems' to address post-traumatic stress issues, ATOD risk reduction, skill building, while using the lessons learned since 9/11 to guide our federal, state and local preparedness efforts in the future. Thus, CSAP is also requesting funds to support its ongoing efforts to help the states develop plans related to terrorism and bio-terrorism and trauma induced substance abuse.

Post Traumatic Stress Disorder: Warning Signs and Symptoms for Children and Adults

Children:

There are a wide variety of symptoms of PTSD, which may vary in number and intensity with each individual. The three categories for this diagnosis include:

- **Intrusive and unwanted memories** - Child may relive the traumatic event through nightmares (may lead to insomnia or fear of going to sleep), flashbacks, sudden memories. These may bring tears and physical distress such as sweating or rapid heartbeat.

- **Avoidance behaviors** - Child avoids any situation or activity or location that might revive memories. Sometimes trauma victims shut down all emotions to protect themselves from painful memories. This can cause the child to withdraw from friends and family, interfere with routine activities, and cause him or her to feel hopeless about the future.

- **Arousal symptoms** - Child becomes jumpy (e.g., overreacts to sudden loud noises such as fireworks) expresses unprovoked anger, is hypersensitive to surroundings ("on guard"), has concentration problems, develops insomnia. He or she may have panic attacks including chest pain, dizziness, rapid breathing, and the feeling they are dying or losing control.

Adults:

Post traumatic stress disorder (PTSD) is a mental disorder resulting from exposure to an extreme traumatic stressor. Symptoms of PTSD are organized within three categories:

- Re-experiencing symptoms
- Avoidance and numbing symptoms
- Symptoms of increased arousal

Re-experiencing symptoms

One set of PTSD symptoms involve persistent and distressing re-experiencing of the traumatic event in one or more ways. In these symptoms, the trauma comes back to the PTSD sufferer in some way, through memories, dreams, or distress in response to reminders of the trauma. A more extreme example of this is "flashbacks," where the individual feels as if they are reliving the traumatic experience. This is more extreme, but less common as a reexperiencing symptom. PTSD is distinguished from "normal" remembering of past events by the fact that re-experiencing memories of the trauma(s) are unwanted, occur involuntarily, elicit distressing emotions, and disrupt the functioning and quality of life of the individual.

Avoidance and numbing symptoms

A second set of PTSD symptoms involve persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness. These symptoms involve avoiding reminders of

the trauma. These reminders can be internal cues, such as thoughts or feelings about the trauma, and/or external stimuli in the environment that spark unpleasant memories and feelings. To this limited extent, PTSD is not unlike a phobia, where the individual goes to considerable length to avoid stimuli that provoke emotional distress. These symptoms also involve more general symptoms of impairment, such as pervasive emotional numbness, feeling "out of sync" with others, or a lack of expectation for future goals being met, due to their trauma experiences.

Symptoms of increased arousal

This set of symptoms is represented by persistent symptoms of increased arousal not present before the trauma. These symptoms can be apparent in difficulty falling or staying asleep, irritability or outbursts of anger, difficulty concentrating, a hypervigililant watchfulness, and an exaggerated startle response. Individuals suffering from PTSD experience heightened physiological activation, which may occur in a general way, even while at rest. More typically, this activation is evident as excessive reaction to specific stressors that are directly or symbolically reminiscent of the trauma. This set of symptoms is often, but not always, linked to reliving of the traumatic event. For example, sleep disturbance may be caused by nightmares, intrusive memories may interfere with concentration, and excessive watchfulness may reflect concerns about preventing recurrence of a traumatic event that may be similar to that previously endured.

ACTING DIRECTOR OF CDC STATEMENT

Dr. FLEMING. Mr. Chairman and members of the Subcommittee, good morning. I'm Dr. David Fleming, the Acting Director of the Centers for Disease Control and Prevention. I'm honored to appear before you today on behalf of CDC, our country's agency that protects the American people by serving on the front lines of public health.

I'll be brief, and try to complement what Deputy Secretary Allen has already told you. Our mind is that although this investment this Committee had the foresight to make before September 11th paid off, the horrible events of that day and the anthrax events that followed demonstrated the need for continued investment in our public health system. We need to be even better prepared to correct the weaknesses we identified and to build the capacities we don't yet have.

So I'm pleased to be here today to testify in support of the President's request for $1.6 billion for CDC, to help guide our Nation's public health activities in this new era.

Our request includes resources to improve CDC capacity, to maintain our national pharmaceutical stockpile and smallpox vaccine stocks, and to continue to improve State and local health department public health preparedness. Let me just briefly talk to you about each of those.

First, for improving CDC preparedness, we're requesting $300 million. This includes a range of activities that improve our laboratories, our surveillance and epidemiologic capacities, our emergency operations ability and research activities. It also includes $100 million for a new laboratory at our Fort Collins facility in Colorado, and to begin to renovate our existing laboratories in Atlanta, which as many of you know, having visited there, are in some need of repair.

During the anthrax attacks, our national pharmaceutical stockpile proved its value by delivering almost 4 million doses of antibiotics to prevent anthrax in 65 deployments to 10 States, with an average time from receiving that request to delivering it in the field of 5 hours. To maintain this capacity for delivering antibiotics and vaccines, including smallpox, we are requesting $400 million. This is $750 million less than appropriated this year. And this decrease results from not having to repeat those large initial purchases of antibiotics and vaccines.

Finally, for building State and local health department capacity, we are requesting $940 million. While only a few States dealt with anthrax illness, the anthrax crisis affected every single State. We saw dramatically how our State and local health departments are the core of our public health system, and how they must be ready to respond to all threats.

The best way to protect against any health threat is to develop our already-existing public health system. That's what we're doing through training, and developing our public health work force, through improving our laboratory facilities, improving our epidemiologic capacity at the local level, by providing secure, up to date information systems and a robust health communications ca-

pacity that includes our health alert network functions and our electronic disease functions that Deputy Secretary Allen asked out.

And I want to assure you, we're being smart with this investment. We're building in measures of accountability. We're preparing for unknown threats by enhancing those systems that deal with known, natural, day to day threats. And we're bolstering State and local health departments' infrastructure that strengthens every single one of our public health actions.

Over the last three months, each of your States has developed a plan for these resources. Please, please talk with your health departments about the needed capacities these dollars are creating in your States today.

In closing, our request represents this Administration's commitment to improving CDC and our Nation's capabilities in preparing for and responding to acts of bioterrorism and other public health emergencies. Make no mistake, this is a tremendously challenging time to be in public health. There has never been a more exciting time to be in this field. And not only at CDC, but throughout this country's front lines, we are ready to do what needs to be done. We are up to this challenge.

In closing, I'd like to thank the Subcommittee for your continued support in protecting and improving our country's public health system. You are making a wise investment. Thank you very much.

[The information follows:]

- Mr. Chairman and members of the Subcommittee. Good morning.
- I'm Dr. David Fleming, Acting Director of the Centers for Disease Control and Prevention.
- I'm pleased and honored to appear before you today on behalf of CDC – our country's agency that serves on the front lines of public health, protecting the American people.
- I'll be brief, and try only to complement what Deputy Secretary Allen has already presented to you.
- Although the investments this Committee had the foresight to make before Sept 11th paid off, the horrible events of that day and the anthrax attacks that followed reinforced, like no other event, the need for investing in our nation's public health system.
- We need to be ever better prepared – to correct the weaknesses we identified and build the capacities not yet developed.
- I'm pleased to be here today to testify in support of the President's budget, which requests 1.6 billion dollars to enable CDC, as part of the Department of Health and Human Services, help guide our nation's public health response in this new era.
- Our request includes resources to improve CDC capacity, to maintain our National Pharmaceutical Stockpile and smallpox vaccine stocks, and to continue to improve preparedness of state and local health departments throughout the country. Let me briefly review each.
- For improving CDC preparedness we are requesting 297 million dollars.
- This includes resources for a range of preparedness activities in improving laboratory, surveillance, epidemiology and emergency operations, and research activities. It includes an increase of 22 million dollars to provide laboratory assistance during large infectious disease outbreaks and to increase our laboratory ability to respond to chemical threats.
- It also includes 100 million dollars to construct a biological laboratory at our Ft. Collins location and to begin to renovate existing laboratories at our Roybal campus in Atlanta, facilities, which most of you know from having taken the time to visit, are in considerable need.

- During the anthrax attacks, our National Pharmaceutical stockpile delivered almost 4 million doses of antibiotics to prevent anthrax in 65 separate deployments to10 different states. Our average response time from request to delivery in the field was 5 hours. To maintain this capacity for antibiotics and vaccines, including smallpox, we are requesting 400 million dollars. This is 750 million dollars less than appropriated in the FY02 emergency supplement – a decrease resulting from not having to repeat initial large purchases of antibiotics and vaccines.

- For building state and local health department capacity we are requesting 940 million dollars.

- While only a few states and cities dealt with anthrax illness, the anthrax attack crisis affected every state. And we saw dramatically how our state and local health department partners are the core of our public health system, and how they must be ready to respond to all public health threats.

- The best way to protect against any health threat is to develop and enhance our already existing public health systems.

- These resources will be used to assure our responses are supported by:
  - a fully staffed and trained public health workforce,
  - strong public health laboratory facilities,
  - enhanced surveillance and epidemiologic response capacity,
  - secure, up-to-date information systems, and
  - a robust health communication capability.

- And we are being smart with our investment. Building in measures of accountability. Preparing for unknown threats by enhancing those proven systems that deal with known, natural day-to-day threats. And bolstering state and local health departments' infrastructure that strengthens every public health action.

- Over the last 3 months, each of your states has developed a plan for these resources. Please consider talking with your health departments about the needed capacities these dollars are being used to develop in your state.

- In closing, our request represents this Administration's commitment to improving CDC's and our nation's capabilities in preparing for and responding to acts of bio-terrorism, other terrorist acts and other public health emergencies.

- Make no mistake. This is also a tremendously challenging time to be in public health. But, there's also never been a more exciting time to work in this field. Not only CDC, but all of this country's public health front lines are ready to do what needs to be done.

- We are up to the challenge.

- In closing, I'd like to thank the Subcommittee for your continued support in protecting and improving our country's public health system. You're making a wise investment.

- Thank you. I'd be happy to answer any questions you might have.

ADMINISTRATOR OF HRSA STATEMENT

Dr. DUKE. Good morning, Mr. Chairman, members of the Committee. I am pleased to appear before you today to discuss the efforts of the Health Resources and Services Administration (HRSA) to further prepare the Nation's health care system and the public health system for possible bioterrorism attacks.

As Deputy Secretary Allen has outlined, the focus of HRSA is to link the health care system with the public health system, so that together we can detect bioterrorist attacks and provide appropriate prevention and treatment. The President's 2003 budget for HRSA proposes that the Agency will operate five programs at a level of $618 million.

I'd like to comment briefly on the hospital preparedness program begun in 2002. For 2003, $235 million, an increase of $100 million, is requested to continue the cooperative agreements with health departments and States and other eligible entities. These cooperative agreements provide funds to States and to our three largest cities to plan and coordinate hospital preparedness. The States and cities are required to pass on 80 percent of the funds to hospitals to expand their capacity to care for victims of bioterrorism.

We recently provided phase one funding, that's 20 percent of the total award, to 59 eligible entities. The grantees used those funds to prepare needs assessments for their areas and develop initial implementation plans. Out of the 59 eligible entities, 53 have already sent in their proposed implementation plans and the other 6 have asked for a short extension.

Just last week, we had a team of reviewers going through those 53 plans, and following our review, the Office of Public Health Preparedness (OPHP) at the Department level will be coordinating a cross-cutting review of these plans as submitted to HRSA and to CDC and the Office of Emergency Preparedness (OEP), to ensure that these plans are coordinated and are mutually supportive, to ensure that we have a strong response capability at the State and local levels.

Two new programs are proposed for HRSA for 2003, the first addresses hospital infrastructure. These are the needs for laboratories, infection control and decontamination and the funding level requested is $283 million. The second would allow HRSA to operate a new educational incentives for curriculum development and training program. That's requested at a level of $60 million.

HRSA has extensive experience in working and collaborating with public and private health professional organizations and academic health centers to develop new and innovative training programs to meet emerging needs. HRSA will continue to operate the emergency medical services program for children at a level of $19 million, and will continue the poison control centers at a level of $21 million. With this set of programs, we believe that we are strengthening the ability of the Nation's public health system and hospitals to prepare for biological or chemical attacks.

Mr. Chairman and members of the Committee, I'd be pleased to address any comments or questions you have on the specifics of any of these programs. I'm pleased to be here today.

[The information follows:]

Spoken Statement by
Elizabeth M. James Duke, Ph.D., Administrator
Health Resources and Services Administration
on
HHS Efforts to Prepare Against Bioterrorism

Before the House Subcommittee on
Labor-HHS Education Appropriations
United States House of Representatives

May 1, 2002

Good morning, Chairman Regula, and Members of the Committee. I am pleased to appear before you today to discuss the efforts of the Health Resources and Services Administration to further prepare the nation's health care system and public health system for possible bioterrorism attacks. As Deputy Secretary Allen has outlined, the focus of HRSA is to link the health care system with the public health system, so that together we can detect a bioterrorist attack and provide appropriate prevention and treatment. The President's FY 2003 Budget for HRSA proposes that the agency will operate five programs at a level of $618 million.

I would like to comment briefly on the Hospital Preparedness Program begun in FY 2002. $235 million, an increase of $100 million, is requested to continue cooperative agreements with health departments in States and other eligible entities. These cooperative agreements provide funds to States and our three largest cities to plan and coordinate hospital preparedness. The States and Cities are required to pass on 80% of the federal funds to hospitals to expand their capacity to care for victims of bioterrorism.

We have recently provided phase 1 funding (20 percent of the total award) to 59 eligible entities.* The grantees used these funds to prepare a needs assessment for their area, and to develop initial implementation plans. Out of the 59 eligible entities, 53 have already sent in their proposed implementations plans. The other 6 have requested extensions.**

Just last week we had a team of reviewers going through these plans. Following this review, the Office of Public Health Preparedness at the Department level will coordinate a cross-cutting review to assure that plans submitted to HRSA, CDC and the Office of Emergency Preparedness are coordinated and mutually supportive of a strong response capability at the state and local level.

Two new programs are proposed for HRSA in FY 2003. The first addresses hospital infrastructure development needs for laboratories, infection control and decontamination, at a funding level of $283 million. The second would allow HRSA to operate the new Educational Incentives for Curriculum Development and Training Program at a level of $60 million. HRSA has extensive experience in working and collaborating with public and private health professional organizations and academic health centers to develop new and innovative training programs that meet emerging needs.

HRSA will continue to operate the Emergency Medical Services for Children Program at a level of $19 million, and continue to fund Poison Control Centers at a level of $21 million. With this set of programs, we believe that we are strengthening the ability of the nation's public health system and hospitals to prepare for biological and chemical attacks.

Mr. Chairman and members of the Committee, I would be pleased to address any comments or questions you may have on the specifics of the programs I have outlined.

* The 50 States, the District of Columbia, Puerto Rico, four territories (Virgin Islands, American Samoa, Guam, and the Commonwealth of the Northern Mariana Islands) and three municipalities (New York City, Chicago, and Los Angeles County).
** Utah, Montana, Texas, American Samoa, Virgin Islands, and the Commonwealth of the Northern Mariana Islands.

COORDINATION BETWEEN AGENCIES

Mr. REGULA. I want to thank all of you. Obviously you're in the front lines of all this. Mr. Allen, I assume you have somewhat of a master plan, if you will, that coordinates the activities of these sub-agencies?

Deputy Secretary ALLEN. We actually do. As you may recall, Secretary Thompson has set up an office in the Department, in the Office of the Secretary, which is the Office of Public Health Preparedness. I know there's legislation going through seeking to request an assistant secretary for public health preparedness. That office is coordinating the activities of these agencies, in fact, Dr. D.A. Henderson is leading that office in the Department, in the Office of the Secretary.

I work very closely with him, though I try to stay out of it as much as possible, but get pulled in often when there are issues that we need to resolve. But we are very coordinated in our work. In my experience in government, at the State level and here at the Federal level, there is an unprecedented level of cooperation within the Department, but also across departments. I think Dr. Fauci has already mentioned our working and addressing biowarfare, it's more than just HHS. It involves the Department of Defense, the Department of Justice and other agencies, in that effort. We're coordinating that as well across the Departments, across the various silos that often exist in Government.

VACCINATIONS

Mr. REGULA. A more practical question, last year we had a shortage of flu vaccines. Now would be the time you would be getting ready for it. Are we going to avoid that in the upcoming winter?

Deputy Secretary ALLEN. We are certainly making every effort to do that. We've seen not only a shortage of flu vaccine, but there's been a shortage of vaccine for equine encephalitis vaccines and the like. This is an issue that we have to address. As a Department, we believe that monies that are being invested in bioterrorism actually serve a broader purpose, that is, as the monies you provided to us in 2002, to address the immediate effects of after September 11th actually served to induce pharmaceutical companies, heretofore who had represented that they did not want to get into this area, of this kind of activity any further, are now rethinking their activities and their efforts in this regard.

So we think that there is an opportunity for us to try to stave off a shortage of flu vaccine and other necessary vaccines. But I'll let either Dr. Fleming or Dr. Fauci add to that.

Dr. FAUCI. Just very quickly, on the point of this impending flu season's vaccine. We are working very closely with the manufacturers. The problem with influenza is that the vaccine needs to be developed each year. The vaccine that was available last year will not protect this year. There is a short timeline, therefore, that the manufacturers have, to determine what needs to be in the vaccine to produce it and to distribute it.

All the indications we have thus far, though, is that the manufacturers are on target to produce at least as much, and probably more vaccine, than was available last year, and better yet, have it

available earlier in the season, that is, in August, September, October, when people are ready to get the vaccine. We're working closely with our private provider network, most flu vaccine is delivered in the private sector, to ensure that they are ready. But we don't anticipate the shortage we had last year.

FUNDING FOR NIH

Mr. REGULA. Dr. Fauci, as you know, this is the fifth year of doubling the NIH budget. Obviously a portion of that doubling money will be diverted to research on bioterrorism, if I understand you correctly. This will then somewhat limit what can be done in some of the other areas, is that correct? And secondly, what kind of research will be focused on bioterrorism?

Dr. FAUCI. You are correct, obviously there is a finite amount of money. The doubling was very generous. A significant portion of the component of fiscal 2003 that went into the NIH doubling is devoted to biodefense, that is correct. As has been the case historically, at the NIH for many years, that when certain issues arise and certain emergencies as we did with the HIV-AIDS epidemic in the mid to late 1980s and through the 1990s, the relative acceleration of one versus another really met not only the public health needs, but in some respects the scientific opportunities. I think we're seeing a bit of that now with the bioterrorism.

In that regard, we fully predict and expect that the positive spinoffs that we have seen when we had disproportionately accelerated one area of research versus another for a variety of reasons, that there are indeed many positive spinoffs. And you know, I've given this Committee over the years many examples of that, not only with regard to the HIV-AIDS, but the various directors of the cancer institutes have shown you how cancer directed research has had extrapolations to other areas.

We feel that the investment in biodefense that the NIH will be making, as somewhat disproportionate as it is, vis-a-vis other areas, will ultimately have positive impacts on everything from emerging infectious diseases that are not related to biodefense, to immune responses of the body to various cancers as well as autoimmune and hypersensitivity diseases.

So you're correct on the numbers, but we think we're going to see the same sort of indirect benefits in other areas.

COMMUNICATIONS

Mr. REGULA. My last question is a two-part. Obviously we don't know where terrorism might strike. Do you have a communications network, because panic would be one of the concerns, so there's a quick response? And as a second part of that, Dr. Duke, you have the community health centers, which addresses the needs of a certain portion of our population. Are you taking steps to enable those agencies to be responsive in the event of a localized terrorist attack?

Dr. FAUCI. Let me address the communication issue. There's really two parts, I think, to your question. First is, in the event of a bioterrorist attack, we, the public health system, need to be able to communicate rapidly and effectively with local health departments, with community providers. The resources that have been al-

located by this Committee to the health alert network and to NEDSS to the State and local infrastructure grants are enabling us to build that integrated, unified communication system that will allow us, using the same system, to deliver health alerts, to transmit data, to provide secure information.

Second, though, an important part of communication is the ability to convey accurate, timely information to the public. We are upgrading our capacities at the Department to do that. In addition, a substantial amount of the resources that are going to the State and local level are going to assuring that they have individuals who are trained, with the messages that need to be delivered. All public health is local. In a crisis, people are going to be looking to national leadership, but they're also going to be looking to their State and local officials to deliver accurate, timely information. We're enabling that through the State bioterrorism cooperation.

Mr. REGULA. If you include the communications, i.e. TV, radio, press, print media, because that's where most of the people look to get their information.

Dr. FAUCI. Mr. Chairman, you're absolutely right. We at the Department level are making connections with the national media.

But it's important that those same connections be made at the State and local level, so that people have pre-existing credibility with the public and with the TV reporters and with the news media. Thank you.

COMMUNITY HEALTH CENTERS

Mr. REGULA. Community health centers.

Dr. DUKE. Yes. In the guidance that we sent out on our grant program for hospital preparedness in 2002, we guided the selection of advisory committees, so that the community health centers would be involved with the development of the State implementation programs, and that is taking place.

Additionally, we collected a searchable data base of all of our community health centers, by State, by zip code, alphabetical order, with all contexts associated with it. And we've also put out guidance to them as well. So we believe they are going to be an integral part of our response.

Mr. REGULA. Did you want to comment?

Deputy Secretary ALLEN. Mr. Chairman, two points I was going to add to that. One, in the Office of the Secretary, there's $5 million that has been appropriated for communications as well. We have established in the Office of the Secretary a command center that will serve as a central point for gathering information from our departments, but also integrating with the rest of Government as well in time of emergency.

As Dr. Fleming has pointed out, under the HAN system and the NEDSS system, one of the requirements of the grants that we're providing the States is that they have to be able to cover 90 percent of their population. And so we can say that with the money you have generously given and we hope and expect to get, we'll be able to cover 90 percent of the population of any State under those systems.

Mr. REGULA. Mr. Wicker.

INCREASED FUNDING

Mr. WICKER. Thank you very much, Mr. Chairman.

I have always been a proponent of increased funding for the agencies represented here. And I don't want to sound like the skunk at the garden party. But do you run into any criticism that this bioterrorism plan is simply a way for you to plus up your agency a little more? And let me tell you what makes me say that, based on the testimony today.

For example, Dr. Fauci said natural causes, he mentioned the flu and AIDS. There's discussion of a broader purpose than just bioterrorism. Dr. Fauci also mentioned indirect benefits. Dr. Curie mentioned with regard to SAMHSA that $1 million was sent to New York City after the attack of 9/11, and yet the attack of 9/11 was a terrorism attack, to be sure, it was not a bioterrorism attack. And a total of only $28 million was sent from SAMHSA.

So I just wonder if you would address that question of how the flu and how AIDS is part of all this. And then let me just throw in my second question, and then the panel can address that, too. What specific acts of bioterrorism are we planning for? And what specific examples in history do we have to go by? Of course, we all know about the anthrax. So you need not mention that.

But domestically, what have we seen in the past, and also, in the whole history of terrorism worldwide, of which we've had a great deal, what specific acts are you looking at for us to go by in addressing these?

Deputy Secretary ALLEN. Sure. To answer your first question, I think that's a very critical question. We would unabashedly say, yes, much of this money will go to plus up our public health system. The reason for that is that when we talk about bioterrorism, the way we look at it at the Department of Health and Human Services, and in our various agencies, is that we're talking about the ability to respond to an outbreak.

In this situation, we talked about the anthrax attacks or a potential smallpox attack or a release of a biological, chemical, nuclear or radiological agent, we look at it in two ways. One, many of these occur naturally. Yet if we're not able to deal with those incidents that occur naturally, it's rare that we will be able to deal with those that occur intentionally. Anthrax was released in this country as an intentional act. It was not an accident. And if we were not able in the most rural parts of this country to address the basic public health infrastructure, allowing them to help survey, to detect and to respond to such an attack, whether it be natural or intentional, we're not serving the purposes of this country and protecting ourselves from what would be a larger, more deliberate act.

So we would not shy away from saying that yes, this money will go to serve in many ways building basic public health infrastructure. But that basic public health infrastructure is the building block upon which our bioterrorism activities are based.

As Dr. Fauci has mentioned, much of the research that is ordinarily being done at the NIH in these areas is going to be enhanced because of the focus on bioterrorism. But it has direct benefits in our attempts to address other infectious diseases and outbreaks that occur.

So we would not be shy about saying that this money is going to address a number of issues that have to seriously be addressed. One being, in the event of a bioterrorist attack, what are we going to be able to do. We would not be able to address that event if we do not have the basic infrastructure.

I'll give you one particular example, and I cite this as the area of how we focus so much on our metropolitan medical response systems are serving our largest cities, 122 major areas. But if we had an event, if we had an agent release in a rural area, we would be very challenged, for the very reason that oftentimes individuals living in rural areas do not have access to primary health care. They do not have transportation, they oftentimes delay seeking care. Thereby, it allows someone who wants to deliberately attack this country to have an opportunity to release it.

Therefore, the weakest links of our system have to become the strongest links of our system. That is what we believe much of this money will go to deal with. But the goal again is to be able to address the bioterrorism event. We could not do that separate and apart from addressing the emerging and re-emerging infectious diseases that we're having to confront.

To address your second question, and I'll ask others to respond to both of these, one example that I can give you is not a domestic example of a deliberate release of an agent, but I do know internationally we've seen this happen. The sarin gas situations in Japan, that would be one that comes to mind very quickly. The fact that we know that Al-Qaeda and other terrorist organizations have trained very deliberately, efficiently, effectively, and at length, in use of biological, chemical, nuclear and radiological agents, while we may not have seen that on our domestic soil here, we do know that it has happened, and we do know that it exists. Therefore, we are trying to be prepared to address whatever that event might be.

Dr. FAUCI. You asked about what threats we are considering. I think one that I mentioned in my discussion that we really need to address is, although it is part of a continuum of emerging and re-emerging diseases, it would never naturally occur. For example, smallpox. It would never naturally occur. And it would be foolish for us not to be prepared for that. We must be prepared for something to be deliberately released on our society here in the United States or someplace else in the world, which would then trigger the necessity for our own response.

And already, as I mentioned in my remarks, the money from the supplement from 2002 has addressed, for example, the dilutional study. Just a few months ago, the United States of America had 15 million doses of smallpox. If we had a multi-focal attack in many cities, which is entirely conceivable, we would have had a very, very serious problem.

Right now, today, we have 77 million doses all ready because of the dilutional study. We have, with the contract with Acambas Baxter, an additional potential likely by the end of this year 155 million doses, and then the Aventis Pasteur additional 75 million doses would put us in a position that by the end of this year, we will have enough, if necessary, to vaccinate each and every American in this country.

So that is a very important accelerated program that resulted from the resources that we were given. That's a very cogent example of one of the questions that you asked about what would be a feasible threat.

SMALLPOX VACCINATION

Mr. WICKER. I know Dr. Curie may want to respond, because I called his name specifically, but what's the downside to smallpox vaccination in terms of that percentage of the population that will have an adverse reaction, perhaps, and contract the disease?

Dr. FAUCI. Absolutely. The downside of the known toxicities of the currently available candidates that we have, vaccines that we have decades of experience with, for every million persons who are vaccinated, there will be one to two deaths per million, and significant numbers of individuals who might have serious toxicities that require treatment that don't result in death. And that's the balance of risk benefit that we have been and are considering and will continue to consider in any policy decisions that are made of vaccinating first responders and/or making vaccine available for those, for example, who would choose to be vaccinated.

Right now the policy, based on solid foundation, is to have what's called a ring vaccination approach, of identifying and isolating cases, and then vaccinating contacts and the contacts of the contacts. That's something that we continually re-examine at the Department, the strategy that we have.

But in answer to your question, the downside obviously of the toxicities, which brings us to the Secretary's long term plan for smallpox, if we had a vaccine now that had virtually no toxicities, I don't think there would be any debate that we would vaccinate everybody in the country with that right now, just because it would be a vaccine that would be easy to vaccinate with very little toxicity. It's the probability and the likelihood of a certain percentage of toxicities that causes us to be very circumspect about a policy decision of preemptively vaccinating.

In fact, we are at the NIH and at the CDC pursuing the research on potential candidates that might not have the toxicities that the classic live vaccinia vaccine has. And when we do have that, I think we'll bring our country much closer to essentially eliminating an important threat of bioterrorism, namely smallpox.

Mr. REGULA. Mr. Sherwood.

Mr. SHERWOOD. Thank you, Mr. Chairman.

On the smallpox, Dr. Fauci and Secretary Allen, you just discussed quite well the ideal situation of what we would do with smallpox if we had the vaccine. But because of the crisis that we all felt after 9/11, I understand that Aventis Pasteur from Pennsylvania donated 70 million doses to the Department of Health and Human Services. This was vaccine that they had produced several years ago, and it was produced really before some of the advances that we know today. And yet that gave us a great deal of security, to have that at our disposal.

I wanted to know why you haven't offered to indemnify Aventis Pasteur with the possibility of your using this old vaccine that they donated to you.

Deputy Secretary ALLEN. Certainly. The vaccine that Aventis Pasteur has donated, of course, would not be used except for an emergency situation. It is 50 year old vaccine. So we're very grateful that they had it. And in times of emergency, we would be willing to use that.

At this point, our legal counsel are working with Aventis Pasteur in terms of the indemnification issues. We're surrounding that. So I'm not prepared to give you an answer specifically as to whether or not that will ultimately occur. But I'll be glad to get a response back to you after having consulted with our general counsel's office that is working with them on this.

This has been an issue, however, in general the issue of indemnification for smallpox vaccine has been an issue that we have been dealing with since and prior to 9/11. It's been an issue that we've been working with the companies, Acambas Baxter, the company that we're working with to produce the 200 million doses, it was an issue then. You may recall the President issued an executive order that included indemnification for allowing the Department to offer indemnification as a means for curing vaccines. So we are looking at that.

But in Aventis Pasteur's specific situation, I can't give you an answer right now.

Mr. SHERWOOD. Mr. Chairman, is that an answer that we could ask to get?

Deputy Secretary ALLEN. I'll be glad to provide that to you.

[The information follows:]

Answer. According to the Federal Acquisition Regulation (FAR), a contractor providing the Government with supplies or services for which it wishes to be indemnified must first submit a formal request for indemnification to the Government. The request must address the nature of the risks for which the contractor seeks indemnification and explain the contractor's exposure to such risks, and must include information on the contractor's existing insurance coverage and the cost and availability of additional insurance. No such request has been submitted by Aventis Pasteur at this time. However, CDC procurement officials and attorneys in the Department's Office of the General Counsel have had preliminary discussions with Aventis Pasteur about the indemnification process.

Mr. SHERWOOD. Fine. Thank you. Thank you very much.

I'll give it back to you, Mr. Chairman.

Mr. REGULA. Okay. Mr. Miller.

ANTHRAX AND OTHER BIOTERRORIST THREATS

Mr. MILLER. Good morning.

When the anthrax things occurred back in October, we read that there was a very limited, first of all it took a lot of technical expertise and specialized knowledge to produce that anthrax. And that there was a finite number of places or people that could handle that. And I know it may cover other agencies, because it's Agriculture and other, FBI and all those.

Are we doing a better job of controlling or keeping track, not only of anthrax, of other potentially bioterror items that could be, because we found out that we thought we had this finite number for anthrax, and it turned out it had been spread around other agencies. And we still haven't solved that problem. But what is being done to keep track of that?

Deputy Secretary ALLEN. I will attempt to answer, and ask Dr. Fleming to further elaborate on it. Under current law, CDC is required to regulate the transfer of certain select agents. There's a select agent list that exists that Congress passed that we would have to monitor. Under the present legislation, the bioterrorism bill, there is additional language that would require us not only to regulate the transfer of select agents, but also to regulate the possession and use of those agents. It goes beyond HHS in terms of CDC and FDA and others in our Department, but also reaches to the Department of Agriculture as well.

In addition, I know the Department of Defense is also looking at working with that select agent list and how they will track the transfer or the use and possession of their select agents also that exist on that list. I'll let Dr. Fleming address in greater detail that issue.

SELECT AGENTS

Dr. FLEMING. Yes, thank you. We take very seriously our responsibility under the current select agent law to try to regulate as best as possible the transferring of these select agents among laboratories, and look forward at the new legislation as enacted to expanding that scope to try to regulate these agents at laboratories that are using them.

There is more that can be done, and we're anxious to work with our partners in the Department and with other agencies to make sure that it happens. The bottom line, though, is that many of these agents are naturally occurring, and the regulation can go a long way to preventing access to these agents by people who shouldn't have them. But we all need to be especially vigilant in that. A regulatory program cannot guarantee with 100 percent assurance that these agents will remain only in the hands of people who are authorized to have them.

CONSTRUCTION

Mr. MILLER. But we are in the process of starting to tighten down some, right. After Oklahoma City, you find it doesn't take always a great deal of sophistication.

Let me switch to another question, Dr. Fauci. The chart over there showed $521 million in construction. Would you talk about that construction money and how that's going to be used, and how much of the total money is really kind of a one time expense and will be available for other programs the next time around?

Dr. FAUCI. Very good question. The facilities in construction are going to be several projects. One is the building of new what we call BSL–4 facilities, which is the highest available containment. There are a very limited number of those facilities in the United States. Currently one in Atlanta, one in Fort Detrick, one at the NIH which is restricted to multiple drug-resistant tuberculosis, one in San Antonio and one that is being built in Galveston.

We are planning to put an additional BSL–4 facility in Hamilton, Montana, which is NIAID departmental-owned laboratory. One in Fort Detrick, in association with our collaboration with the Department of Defense, as well as a variety of regional centers of excellence in biodefense and emerging infections, that will have BSL–

3 facilities in them, and where appropriate, perhaps one or two additional BSL–4.

So it will be the construction, but also it would be the training of individuals who will be part of that process, because you will have to train an additional generation of individuals who are skilled in working in these very special circumstances.

With regard to one time money, indeed, for the building itself it would be, but a substantial amount of money, for example, that one year would be allocated to the building itself, and a relatively smaller amount for actual research to be conducted in that building, because the research can't be conducted until the building is up, that the subsequent out years, money that was put in for the building would then be money that would actually be put toward the research to be conducted.

So although there may be part of the money that could be "freed up" because it's one year money, the plans, the three and four and five year plans that we have, will in fact utilize some of the original one year money to actually be money to support the research. So at the end of a four or five year period, you actually would have money that would be continued from one to the other. So although there's the possibility of some of it being freed up, I don't think it's going to be a substantial amount that will be freed up.

Mr. MILLER. Thank you.

Mr. REGULA. Mr. Cunningham. I'm sorry, Ms. Pelosi.

SMALLPOX

Ms. PELOSI. You know what the system was, Mr. Chairman. We're under the 10 minute rule, right?

Thank you very much, Mr. Chairman. I really want to commend you for having this very, very important hearing. It's a very special one, in that it is cross-cutting, across so many different agencies, as you so wisely planned. And I think very valuable.

I of course am very interested, from the standpoint of this Subcommittee, but also as the ranking member on the Intelligence Committee. I'm very pleased with what I heard, but I have some questions as well, that have arisen from my other work beyond this Committee. And I want to follow the line of questioning that Mr. Wicker was pursuing about the smallpox vaccine. I understand the answers that were given, and clarifications Mr. Sherwood had sought.

But I wanted to ask you, I was interested, Dr. Fauci, that you said that one in a million people could die. I mean, God forbid that one person should die, but that's a small number compared to, I've heard one in 25,000.

Dr. FAUCI. No, it's not that much.

Ms. PELOSI. But a large number could have symptoms?

Dr. FAUCI. Right.

Ms. PELOSI. I've heard encephalitis, or other bad consequences from the live vaccine, smallpox vaccine.

Dr. FAUCI. Correct.

Ms. PELOSI. I wondered if you are doing any research or, if you had the money would you want to do the research, for a dead smallpox vaccine which I understand is less harmful?

Dr. FAUCI. Yes, Ms. Pelosi, thank you for asking the question. This is an important part of what we call the third generation smallpox. The first generation is what we have, that dry vaccine that we got from calf lymph, that we diluted, the study that I referred to. The second generation is the same microbe, but developed in tissue culture and not in calf lymph.

The third generation is exactly what you're referring to, and that is part of our intermediate to long range plan to examine either highly attenuated or killed versions of the smallpox, there's one candidate that seems promising called modified vaccinia ankara, MVA, we refer to it as. Modified vaccine ankara, like in Ankara, Turkey, MVA.

It is actually promising because it has been used as a vector, it's a virus as a vector to carry the genes of other viruses, and has been used, for example, in certain studies in cancer patients where you vaccinate cancer patients against certain of the antigens of their own tumors. So the cancer people have a lot of experience in that regard.

But the one thing that they've learned which is of keen interest to us in the infectious diseases field is that there have been very little, if any, of the toxicities that we have seen with vaccinia. We have not seen that with MVA.

So now we need to prove, and we are in the process of addressing that now, that if you vaccinate someone with MVA, A, is it safe, and I can tell you right now that it is, because we've done a lot with people who are not being vaccinated for smallpox. But the other, does it induce the potency of an immune response that we just recently showed over the past few months when we did the dilutional study with vaccinia?

If both of the answers to those questions are yes, then we're going to very aggressively pursue that. That's the point that I made in answer to one of the other questions. If we had in our hands now a complete safe, effective vaccine against smallpox, the whole dynamics about when and who you would vaccinate would change very rapidly.

Ms. PELOSI. And do you have the resources to move to this third generation?

Dr. FAUCI. Yes, in the plan, and again, this gets back to the question that Mr. Miller asked, in the three and four year plan that we have about the resources that we have been given now, and we will use in subsequent years, we would have the money to do that.

Ms. PELOSI. But if there's scientific opportunity now and the toxicity is less, why aren't we moving right into it?

Dr. FAUCI. We are. But the studies will take a couple of years to do.

Ms. PELOSI. Let me just follow up on that, and I appreciate everything you're saying. Now, would this, how would this be different for people with compromised immune systems already?

Dr. FAUCI. They are the main people, one of the main groups that we're concerned about. So if you have a non-live vaccine, that it is virtually impossible for that microbe to get out of control in someone who is immunosuppressed, the big problem with vaccinia is that if I were immunosuppressed and you vaccinated me, my

body's normal defenses, which would respond to the vaccine, make a good immune response and then protect me, might not even be able to suppress the actual vaccination itself, which would then cause a disseminated reaction in me.

That would essentially be a non-issue in a vaccine——

Ms. PELOSI. Dead vaccine.

Dr. FAUCI. Yes.

EMERGENCY MEDICAL SERVICES FOR CHILDREN

Ms. PELOSI. Thank you. I have one quick question, and I'm going to address it to Secretary Allen, and thank you all very much for your very excellent presentations. I wish I had time to ask you all my questions.

Last year with the cooperation of our great chairman, I was able to get $10 million in our bill to assist communities implementing emergency response evacuation, parental notification plans for schools and other community facilities where children gather. We were told in our community, whether we talked to the police, the fire, first responders, they all said the same thing, protect the children. We have to have a component to protect the children first.

And I wondered what role the emergency medical services for children played in the effort to protect schools. Is HHS collaborating with the Department of Education in this effort?

Deputy Secretary ALLEN. We are collaborating with the Department of Education in this effort. To give you another idea of where some of the other monies that are going to serve this purpose, back in, I guess it was January, I had the privilege of going to Colorado, I was in Colorado Springs where some of our metropolitan medical response systems, they were actually conducting an exercise. At this particular exercise, they had the broad range of the types of first responders there, but they also had the media included, public utilities and education, they had the Department of Education represented there.

So these are the sorts of exercises that we need to continue doing, and the monies that have been appropriated have served for that purpose, of making sure that Health and Education are working together to address the needs and concerns, particularly as they relate to children.

Ms. PELOSI. I appreciate that, and I look forward to working with you on it. Thank you all very much. Thank you, Mr. Chairman.

Mr. REGULA. Mr. Cunningham.

ANTHRAX EFFECTS/STUDIES

Mr. CUNNINGHAM. Thank you, Mr. Chairman.

I, like Ms. Pelosi, sit on the Select Committee on Intelligence. So we know exactly what the threat is now, but what in many, many different countries on recent briefs that we've had, on a gearing up of Al-Qaeda in bio and chemical, biological warfare that could be eminent, there is a rapid movement even as we speak today in a real global threat. So I laud your efforts in what you're doing, as Ms. Pelosi does.

One of the concerns I have, I also sit on the Defense Appropriations Committee—busy guy. But one of my concerns was, say, with anthrax vaccinations in the military, is that there wasn't enough

studies being done. For example, we have more and more women in the military. What were the effects of anthrax vaccinations if the woman should become pregnant? And those kinds of studies, this Nation put a lot of men and women on the front line with an A-bomb and you see the results.

When you look at Agent Orange and the results that our Nation did to a lot of our veterans, if you look at Desert syndrome and where they denied that there was anything, when we have all of the evidence that there is something wrong with these folks, my concern is that as we move forward, sometimes—I want to move fast, like you do—but we don't have the safeguards to protect our men and women with these new biological retreats that we have, such as anthrax, such as smallpox, such as these things that go forward.

Second concern, and which I'm glad, you gave a good example with smallpox, my concern, the military is charged with fighting two fronts. But if I was a bio and chemical terrorist, I would load a load of marijuana or heroin, and can you imagine the influx in our inner cities, and maybe loading it with hepatitis-C or with Ebola, those kinds of things, where you not only vaccinate those people but just the exponential expansion of the disease would be bad.

I've seen software that right now focuses in directing fire, police, Centers for Disease Control, all of those things, and you did talk about how that you're working together, but I think we still have a long way to go in that. I guess my real question is, are we looking, with these new technologies, to safeguard that we're not actually doing more harm in vaccinating and taking care of the public in these threats?

Deputy Secretary ALLEN. A couple of responses, and I'll ask both Dr. Fleming and Dr. Fauci to respond. That is certainly a concern that we have, first of all, from human subject protections, as a Department, we're very concerned about that issue, ensuring that whatever we would do, whether it's in a time of emergency or in a non-emergency situation, that we protect humans, their health and safety. That's the utmost goal of the Department.

So in doing that, particularly in this regard since we're looking at vaccines, the reason why we've requested funding for the NIH and for CDC is to actually conduct those types of studies. The reason why we've got the Aventis Pasteur gifts that they've given us in terms of the 50 year old vaccine, we know how that was created, we know that it has certain impurities in it, and therefore, we reserve that for only an emergency situation, yet we're still conducting tests to make sure of the efficacy of it.

PUBLIC HEALTH PREPAREDNESS

Mr. CUNNINGHAM. If I could interrupt you just one second, that little yellow light goes on and my time is up.

Another question is, where my colleague said, does it appear that you're trying to beef up, I had a brief, and are aware that you've actually sent teams to Asia where the flu starts. Many scientists feel that 1918 is going to emerge within the United States and the world again. I would think that if anybody criticizes you for the ef-

forts of this Committee, trying to keep in line the requirements that you have, then I think the alternative is very deadly.

Deputy Secretary ALLEN. Point well taken. And again, we would not be bashful about saying, yes, we're beefing up, because we know that again, the basic public health preparedness is what is going to protect us in the time of an event.

I do want to finish and give Dr. Fauci and Dr. Fleming a chance. But I will say, you've raised a question about DOD. We work very closely with the Department of Defense in coordinating and looking at these issues, much more closely now than perhaps we did in the past. There is coordination and cooperation on these sorts of efforts in terms of having tests performed, research done before we actually vaccinate anyone.

ANTHRAX VACCINATIONS

Mr. CUNNINGHAM. If you could just look into anthrax vaccinations for especially the military to see if there is effects with women that may become pregnant. It's a real concern.

Dr. FAUCI. Just an extension of that, Mr. Cunningham, the agenda for research for development of vaccines is not only for vaccines for diseases for which we don't have an existing vaccine, but improvements for the vaccines that we already have. Two good examples, one you mentioned, one that was in response to a question by Ms. Pelosi, and that is the smallpox vaccine that would be as effective but not attenuated, essentially, so attenuated that it just wouldn't cause any problems.

So if we would have a vaccine that would be safe, we would eliminate all the concern about that. With regard to anthrax, the currently used vaccine is called AVA, for anthrax vaccine absorbed. That is one that's made from the supernatant of a culture that has a lot of elements in it, some of which might not even be needed to induce immunity.

The currently tested one that we're in the process of right now testing for the next generation of anthrax is what we call a recombinant protein, a recombinant protective antigen, which is just one of the elements of the original, more crude vaccine for anthrax. When we prove that to be safe and immunogenic, you can almost guarantee that toxicities of that more highly purified vaccine will be less than what we've seen in the more crude ones.

So a lot of the effort that we're talking about, all of us today, are geared towards improving vaccines for the purpose that you mentioned, to make them safer.

Dr. FLEMING. Just one last quick comment, is that while we're awaiting this new generation of anthrax vaccine, there are dollars being requested today to allow us to specifically address the questions that you're asking regarding safety of the existing vaccine. Those studies are going on.

Mr. CUNNINGHAM. Thank you, Mr. Chairman.

Mr. REGULA. Thank you. Mrs. Lowey.

HOSPITAL PREPAREDNESS

Mrs. LOWEY. Thank you, Mr. Chairman. And I want to thank our presenters for your testimony today.

My first question is about hospitals. Hospitals will undoubtedly be the first impacted in a bioterrorism event. But as we saw with the anthrax outbreak in New York City, our hospitals are simply unprepared. Emergency rooms could not handle the amount of people who came in convinced they were exposed to anthrax.

Right now in New York, most hospitals are running at full capacity. One hospital's CEO reportedly gave up his office recently to provide space for patients.

Now, you can't chalk this up to poor management, it's the result of HMOs and ever-shrinking Medicare reimbursements, forcing hospitals to eliminate excess capacity. Other States face the same situation. Hospitals simply cannot afford to keep beds open or stockpile supplies in case of a bioterrorism event. And I can assure you that $618 million is not enough to help our hospitals prepare.

The estimated costs, as I understand them, to hospitals, to fully prepare for bioterrorism, is over $10 billion. I'm glad to see that head shaking and agreeing with us. So my question is, is the Administration interested in a long term solution? Is this a short term fix? Is the Administration looking at the larger issues facing hospitals? Has it asked them to take on responsibility? Just to Secretary Allen, thank you.

Deputy Secretary ALLEN. Yes, no, yes. [Laughter.]

The Administration is interested in this issue. In fact, the reason I nodded is that we are too aware of what the hospitals are saying that it would take for them to be prepared, $10 billion. And we're not arguing with that figure.

What we are saying though, is that in the interim, what we're doing is the $618 million, we have $518 million, is what I have, is a significant investment in what we need to do immediately to help work with and to address these issues.

We are going to be working with them very closely, and I want to ask Dr. Duke to address specifically how the $518 million is trying to go and focus on building capacity, building regional cooperation and helping to bring training to those who are really going to be on the front lines in the hospital systems to address that. I do want to say at the very end of that that we also would say that we think it's important that the HMOs and health plans are also a part of our preparedness as a Nation, as opposed to them being a part of the problem, that they will also be a part of the solution.

Dr. DUKE. Thank you. In our proposal for this year, we have two programs. One is the hospital preparedness program itself, which asks for the States to put together a comprehensive program working with their hospital associations, working with their offices of rural health, working with a broad scope of providers of health care, including for example, the health centers as well.

We've asked them to work on a regional approach, rather than simply the "lonely bandito" approach of one hospital at a time, but rather to work in a coordinated fashion. We've also put in a program for capital investment to improve emergency rooms, to improve the capacity of hospitals to meet emergencies involving 500 patients or more. So with the regional approach and with an educational approach, we are looking also at investing in our training capacity, so that the new diagnostics that are coming up, the new

treatment modalities that are coming up, are available to the first line folks in the hospital setting.

So we believe we're making the appropriate investment as a beginning step here to get up to speed. Next, the capital investment plus the hospital preparedness program, we believe, will make a tremendous contribution toward improving our capacity to respond.

STATE AND LOCAL PLANS

Mrs. LOWEY. Did I hear you say that you're working with the States to put together plans?

Dr. DUKE. Yes.

Mrs. LOWEY. And are you, maybe you can expand on that. Are you working with the States in ensuring that the States are coordinating with local governments? Because I know, I attended a meeting with my local hospitals, for example, and I'm working closely with my local government in trying to make sure we're prepared. Boy, there's a lot of work that has to be done. So I just wondered if you could elaborate on that.

Dr. DUKE. Yes. The approach we've taken is that the funding is going through States with a responsibility to ensure that all of the relevant actors are involved, hospitals. The requirement in our guidance is that 80 percent of the funding will be immediately passed through to the hospitals who will then work with their partners on the local level and on the regional level. We at the Department level will be working with our colleagues to ensure that the money that is provided to CDC is coordinated with what's available through the emergency preparedness that's available through HRSA.

So we believe that we are getting synergy out of the funds that you've provided to make these big steps forward. So the States are absolutely crucial, because health is a locally provided service.

Mrs. LOWEY. Is there a time frame within which they're supposed to be reporting back? And then is there an evaluation of these plans?

Dr. DUKE. The plans have been coming in, the first set of plans was due on April 15th, and 53 of the 59 eligible entities have provided initial plans. We're in the process of reviewing those plans right now. And each agency will review them from the point of view of the guidance relative to the program they have. But in order to ensure the kind of coordination at the national and the State and local level, those plans, as reviewed by, for example, HRSA, under the hospital preparedness program, will then be reviewed yet again by a cross-cutting committee headed by D.A. Henderson's office of Public Health Preparedness. Those plans then will be coordinated to make sure that we're getting the maximum impact for our investment. That's happening right now.

FUNDING FOR STATE AND LOCAL PLANS

Mrs. LOWEY. I see the red light blinking, so just one other quick one, Mr. Chairman. After you review the plans, will there be additional money going to respond to the needs in the plan?

Dr. DUKE. Yes. Twenty percent of the funds were made available for planning and immediate implementation. The other 80 percent will be going out by early summer.

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

Mr. REGULA. I want to advise the members that I think we'll have time, Mr. Istook has yet to take his time, but we'll have enough time that each member could have at least one additional question, if you would like, before we adjourn. So, Mr. Istook.

SMALLPOX VACCINATION

Mr. ISTOOK. Thank you, Mr. Chairman.

I really just have one simple question, with a little bit of a prelude. I understand, of course, the ring method for eradication of smallpox and similar strategy with other diseases. I understand also of course that our society is much more mobile than the third world societies where the final round of eradication occurred. We of course have had significant vaccination programs as far as the suppression of the disease in earlier years.

I am still concerned about the potential success of the ring approach to a mobile society such as ours if we were to have some sort of terrorist induced outbreak such as smallpox. I'm concerned that the ring theory would not be near as successful without a potential high mortality rate in a society with as much mobility as we would have. I therefore question whether we should rely upon that to the extent that I'm hearing.

With that in mind, knowing that we have vaccine stockpiles, understanding the concern with toxicity levels, especially among those that have a depressed immune system, and therefore people may not wish to start a national inoculation program such as we haven't seen for many years, I guess the last national major one was maybe, was it swine flu in the Ford Administration? But what is wrong with the approach of making the stockpile that we have available to those who wish to have inoculation, to let members of the American public who want to have the inoculation for themselves and their family, not as a massive program trying to make sure that everyone is, but at least diminishing what the potential impact might be, on a voluntary basis, but making our supplies of vaccine available for that?

Deputy Secretary ALLEN. As an initial start, and I'm going to ask Dr. Fleming and Dr. Fauci to address it, the first issue is, we need to have ample supply before any discussion about that would ever occur.

Mr. ISTOOK. That's a hundred million and the others that are being expanded?

Deputy Secretary ALLEN. Correct. We have 300 million citizens, so therefore you start down that path, who gets it, how you ration it. It creates the very issue of risk communications that we've been trying to address.

Mr. ISTOOK. Presupposing that everybody wanted to affirmatively seek it.

Deputy Secretary ALLEN. Correct. Then beyond that, I think there are other issues that we need to address, and I'll ask them to address them, but there are some international issues that we need to address as well, is that of course, as the United States would begin a process of that, we have certain obligations to allies. And it raises some other issues that we have yet to address.

In fact, the week after next, the World Health Organization will be meeting, the World Health Assembly, and this issue is on the agenda to discuss. So I think there are issues that go beyond simply having the supply available, first and foremost, and then making that decision as to whether to have voluntary or involuntary strategies, that both have certain risks and benefits associated with them.

Mr. ISTOOK. But basically you're saying the stockpile that most Americans have been told is intended for our protection, that we can't make those decisions unless we decide whether other nations in the world want to draw upon our stockpile?

Deputy Secretary ALLEN. Absolutely not. That is not what I've suggested nor is that what I've said. What I have said, though, is that we have to balance the benefits and risks associated with a decision such as that. Because for example, we do, as you've already stated, we live in a global community, and largely the mobility is a major issue. Therefore, an outbreak of smallpox anywhere is an outbreak of smallpox everywhere. So we have to be prepared to address that.

But to get more specifically to your concerns about the addressing of the strategy, the ring strategy and where we go from that, I'm going to ask Dr. Fleming.

Mr. ISTOOK. In that mobile society, correct.

Dr. FLEMING. A couple of points. First, I wanted to assure you that we recognize that this is a controversial issue, and one that needs further discussion. So we are going to be embarking, over the next three to six months, in some national dialogue on this, using our immunization experts and involving appropriate community providers as well, so we can come to a solution.

But let me comment specifically on ring vaccination. In fact, smallpox was eradicated from Europe well before it was eradicated in Africa. There were multiple instances in the 1970s and 1980s where it was reintroduced into the European population, that is reasonably mobile. And in that setting ring vaccination was able to effectively contain the epidemic.

Mr. ISTOOK. But it was still among a population that had had a lot of inoculation?

Dr. FLEMING. Yes, although inoculation in any of those instances had been discontinued. So a fair proportion of the population was naive.

Having said that, we do believe that the first approach to containment does need to be ring vaccination. We are preparing our State and local health departments around the country to recognize and respond, to deal with the mobility issue. That's not to say that in a worst case event, if ring vaccination was failing, that we would not quickly move to an additional strategy.

One last point. The issue around choice, and shouldn't people be allowed to get the vaccination if they want it, is it an important one. And as I say, we are going to be having this national dialogue on that. I would point out, though, that the risk of vaccination is not just to the individual who receives it. Because it is a live vaccination, someone who has been vaccinated is capable of transmitting that to individuals around them.

So in the setting of vaccination, we would expect transmission of the vaccine strain to others around vaccinated people, including immunocompromised individuals. And in that context, we do need to weigh in that it's not purely an individual decision, whether to be vaccinated, but rather in part a societal decision as well, taking into account the risks to people who did not want to be vaccinated but who were inadvertently exposed to someone during the time that they were infectious after receiving vaccine.

HOMELAND SECURITY

Mr. ISTOOK. I appreciate the information, and I certainly just want to finally stress that a major aspect of all of homeland security is expecting people to assume burdens and responsibilities for security rather than expecting it to be simply a government agent at the airport or whatever it may be. The private sector is having to assume a lot of responsibility, individuals expect that they have to assume a lot of responsibility.

And as I mentioned, I think that one thing we need to factor in intensively in this is, are we just going to have homeland security that is a Government program saying, everybody should/must do this as far as an inoculation, for example? Or do we say, we want to be enablers for people that do want to heighten the security levels for themselves and their family, and therefore deal with, and I don't know if the inoculation has to be a live strain as opposed to a dead strain, the technical part of that I don't know.

But I think there are serious questions here about the overall approach to homeland security, to what extent is it going to be Government driven and to what extent do we expect the average American citizen to be accepting responsibilities?

Deputy Secretary ALLEN. Those issues are being discussed very vigorously within the Executive Branch, not only within the agencies working with the scientific community, but also I know on the homeland security council we are discussing those issues as well. So I do want to make sure you understand that we are very much trying to get our hands around these issues.

Mr. ISTOOK. Certainly.

Deputy Secretary ALLEN. Because they do have serious implications. And in many ways, I think your point is well taken, that it's not always a Government solution. That's certainly what we've learned in trying to respond to innovating. And that's very much of the reason why we're asking for the funding we're asking for, is both for intramural programs and extramural programs. Much of that also revolves around these sort of questions of what is the most appropriate strategy to adopt in terms of how we deal with an outbreak.

I was in London the earlier part of April at a G7 conference where we gathered together with some of the G7 states, in addition to Mexico, to talk about these issues, again, how we're going to approach it in terms of approaching the World Health Organization as well. So these issues are going on at all different levels, because we have great concerns and a need to be concerned. So they will be weighted very seriously.

Mr. ISTOOK. Thank you. Thank you, Mr. Chairman.

PREPAREDNESS

Mr. REGULA. Mr. Allen, just a summary. Are we much better prepared today than we were on September 10th to deal with all of these possible impacts of terrorism? And secondly, will a lot of this work that's being done, i.e., communications, improving the public health system, have a benefit to society in addressing other things that result from natural causes, result from, like in our instance, in our area we had a meningitis outbreak, they had Legionnaire's disease in Cleveland. Will we be as a society much better prepared, even if it isn't terrorism? And if there is, do you think we're in pretty good shape?

Deputy Secretary ALLEN. I would say in terms of being prepared vis-a-vis September 10th or 11th, I would say absolutely. We have worked together, because of your efforts here in Congress in providing funding for us, and we've worked across Government both at the Federal, State and local levels, with the private sector, and with communities. I would say yes, we're much better prepared.

Are we absolutely prepared? No. There's much work still to be done, particularly, for example, as we talked about earlier in terms of making sure that the weakest links of our systems are the strongest links of our systems. We need to be reaching into communities to make sure that they understand the significance and how they can be prepared in addressing these sorts of issues.

In terms of where we are, the spillover benefits are great, as we've already talked about, the fact that we will have a BL-3 lab and a BL-4 lab in Montana. I was in Hawaii last week visiting some of our folks there. They will be having a BL-3 lab in Hawaii to be able to address, as offshore. Some of the issues they're dealing with are dengue fever, tuberculosis, leprosy, something that we don't even think about on the mainland. These are issues they're confronting.

And because of the investments that have been made, using bioterrorism as the impetus to get money into the system, we will improve the ability to provide public health care, population based public health, research and coordination across the board. There's no doubt that this money has served and will serve a very valuable purpose to better prepare the American people for whether it's a terrorist attack or a natural outbreak of disease. These are issues that we must be prepared for and we're grateful for the monies.

Mr. REGULA. A good investment.

Deputy Secretary ALLEN. Absolutely.

Mr. REGULA. I would advise the members of the Committee, we do have another panel. We have the Agency for Health Care and Research Quality. However, I'm still going to give our members any additional questions they would like to ask. Because what you're doing is extremely important. This is very significant.

Deputy Secretary ALLEN. And I don't want to discount, if I can, Mr. Chairman, because you do have the Agency for Health Care Research Quality coming up, I want you to understand that they're involved in this effort as well. As the private sector has been coming to the Department with technology, with experience, with knowledge, we have had to be a conduit to link the public and HHS

as a whole with what they're doing. So I want to make sure that link is there as well as you talk with them on this issue.

Mr. REGULA. Mr. Sherwood, anything additional?

HEALTH CARE

Mr. SHERWOOD. Yes. I'd like to make one little comment. Dr. Fleming, in World War II when the country was really concentrated on what we had to do to get through that, we made some technology jumps and some organizational jumps that have served us very well in the ensuing 60 years.

Now that we are very concentrated on bioterrorism, is there going to be some serendipity there? Can we use that to increase the linkage between our new knowledge, our research like NIH and CDC, to health care delivery? Example, an article in the Post this morning about beta blockers and how important they are, and yet so often they're not prescribed. Are we going to make some jumps out of this that are going to do us some good in the long run, where our efforts to fight bioterrorism, are we going to get some serendipity out of this?

Dr. FLEMING. I'd like to comment as well, I sure hope it won't be serendipity, but yes, is the short answer, that we are consciously trying to make those things happen. Without going into a lot of detail, just one example in health care delivery, one of the major problems we're facing is the delivery of preventive services to adults. That's something that is hard in our clinical system to make happen.

One of the benefits of these dollars is to increase the existing linkages between health departments who have that as a priority and the medical community. So certainly, one of the intended outcomes here is not only to make those connections so that providers will be better able to respond to a bioterrorist event, but to increase the credibility in the linkages between the public health system and the medical community, which will result in, for example, better delivery of adult preventive services, immunizations, influenza vaccine, pneumococcal vaccine, a whole host of secondary benefits.

Mr. SHERWOOD. Thank you.

Mr. REGULA. Mr. Miller.

Mr. MILLER. No questions, Mr. Chairman.

Mr. REGULA. Mr. Cunningham?

RESOURCES

Mr. CUNNINGHAM. Just one statement. One of the things that's overlooked in coordination of the different groups, to be able to help in case of a national emergency, some of the members on the Floor tried to eliminate the Selective Service System. They don't believe in Selective Service or the draft. The draft would only come in case of national emergency, like a world war. But one of the things that the Selective Service does do, it coordinates and has lists of all of those individuals that have specialties to help in case of national emergency, like bio and chemical warfare.

I would hope that you would work with those groups as much as you can, because it's a resource for you that many people overlook.

Thank you, Mr. Chairman.

Mr. REGULA. Mr. Istook.

Mr. ISTOOK. No further questions, thank you.

PUSH PACKS

Mr. REGULA. On push packs, are they out in place now?

Dr. FLEMING. Yes, the national pharmaceutical stockpile has 12 locations around the country where those push packs reside.

Mr. REGULA. Within them, they have a lot of what would be needed in any given locality in emergency?

Dr. FLEMING. Fifty tons of equipment in each, and then in addition, there's a backup or reserve to supplement, after the first 12 to 24 hours. We can get push packs to any place in the continental U.S. within five hours of receiving the request, excuse me, six hours.

Mr. REGULA. So that would be an enormous advantage in the event of a crisis, either terrorist or otherwise.

Dr. FLEMING. Absolutely.

INTER AGENCY COORDINATION

Mr. REGULA. Second question. Does the military, and the work they're doing, you mentioned anthrax, do you coordinate so we're not reinventing the wheel? Because you have a broader range of challenges, but nevertheless, a lot of what the military's probably doing has a value in the civilian side.

Dr. FAUCI. The current project on the development of a second generation anthrax is being done in total collaboration with the Department of Defense currently and in the future.

Deputy Secretary ALLEN. In addition, as you are aware, in case of a national disaster, under the National Disaster Medical System, the military, that would be DOD, the Veterans Administration and FEMA, report to the Secretary of Health and Human Services. So on September 11th, we enacted a public health emergency under Section 319 of the Public Health Services Act. They reported up under to the Secretary.

In fact, two weeks ago, Secretary Thompson met with all the surgeons general of the various branches of the military to again discuss this coordination across Government. So that's a key element, that in times of need, their resources would come to bear if they weren't fighting on a second front. So those are issues that would be very important in times of national emergencies.

Mr. REGULA. And lastly, I assume you coordinate with Governor Ridge?

Deputy Secretary ALLEN. I'll be meeting with him later on—regularly.

Mr. REGULA. Okay. Thank you very much. You've been very informative, very instructive, a lot of information this morning.

BIOTERRORISM PREPAREDNESS AND RESPONSE

Mr. Regula: How will the funds provided to the Department for FY2002 and requested for FY2003 improve access to information by the public regarding bioterrorism preparedness and response?

Mr. Allen: The CDC Guidance for FY2002 Supplemental Funds for Public Health Preparedness and Response for Bioterrorism directs states to develop preparedness in six focus areas. Focus Area F is entitled "Communicating Health Risks and Health Information Dissemination." In their required work plans, states have designated $39 million for this focus area. These funds will be used to ensure that state and local public health organizations develop an effective risk communications capacity that provides for timely information dissemination to citizens during a bioterrorist attack, outbreak of infectious disease, or other public health emergency. Such a capacity includes training for key individuals in communication skills, the identification of key spokespersons (particularly those who can deal with infectious diseases), printed materials, timely reporting of critical information, and effective interaction with the media.

A critical benchmark in this area is development of an interim plan for risk communications and information dissemination to educate the public about exposure risks and effective public response. Projects were required to submit this interim plan with their work plans, due April 15 of this year.

Mr. Regula: There seems to be some confusion about the $250 million included in your FY03 budget for anthrax vaccine. What do you expect that funding to be used for- development or procurement of the vaccine?

Dr. Fauci: The new generation anthrax vaccines are not currently "off the shelf" items. These vaccines need to go through a development process before they can be purchased. It is important to appreciate the complex nature of vaccine development and the relationship of initial development of candidate products to the production and purchase of the end product. First, there is the development of the candidate vaccine as a proof of concept. This is actually a series of endeavors that takes the candidate product from basic research through pre-clinical testing to early clinical testing to show that the candidate product will be safe and work as intended in humans. Second is the manufacturing process development of the vaccine product. This activity requires significant investment, and includes scale up of the production of the product from pilot lots of a few thousand doses to producing millions of doses under Good Manufacturing Practices with extremely tight manufacturing tolerances. This is usually the most expensive area as it requires designing, developing and building the physical production plant, consistency testing of multiple batches of vaccine, product validation studies and clinical trials to provide the product and clinical data needed for licensure of the manufactured product by the FDA. The final stage is the actual production and distribution of the manufactured product.

There are three points that should be considered as we move forward in our efforts to develop, test and purchase the new-generation anthrax vaccine candidates. First, the anthrax vaccine candidate is still under development and not available to be purchased "off the shelf." Second, the development and testing of the new-generation anthrax vaccine is under an extremely tight schedule. Third, the process of vaccine development is inherently unpredictable. We do not know what developmental challenges may yet be encountered with these vaccine candidates. In this regard, although the $250 million will go towards investment in the second-generation anthrax vaccine product, it is difficult to project the precise proportion of the $250 million that will be used for development, under a manufacturing setting, versus "purchase" of the product off the production line.

ANTHRAX VACCINE

Mr. Regula: How long do you expect it to take to complete the clinical trials before the anthrax vaccine can be purchased?

Dr. Fauci: A promising new generation anthrax vaccine, recombinant protective antigen (rPA), has been under development for several years within the DoD with NIAID support. NIAID recently produced a clinical lot of the vaccine and is collaborating in clinical development of the vaccine. However, additional product development and testing will be required before this promising candidate is ready for production and licensure. NIAID published an RFP on April 22 for work to accelerate clinical development of a licensable rPA vaccine, a process that should allow production of a product that would be suitable for emergency use under IND in 2004. We currently anticipate a course of action comparable to that taken for the smallpox vaccine. Once we are reasonably confident that the clinical trials will show the vaccine safe and effective we would begin production and commit to the buy before completing trials. That is why the budget requests $250 million for this work.

Mr. Regula: Isn't procurement of vaccines predominately a function of the CDC? Why then does the budget request propose to have NIH involve itself in vaccine procurement?

Dr. Fauci: The nation has an urgent and compelling need to have a second-generation anthrax vaccine product available as quickly as possible, but at the moment, one must still be developed and tested. Given that the research, development, clinical testing, and procurement of a second-generation anthrax vaccine are very closely linked activities, and given the need to accelerate these efforts, we believe it makes a lot of sense to have all of this carried out in one place through NIH. NIH has been given this task in line with its successful track record in the development and testing of other vaccines. NIH will not, though, become a stockpile manager for this vaccine. When it is ultimately purchased, the vaccine will be managed by CDC as part of the national stockpile.

BIOTERRORISM

Mr. Regula: Dr. Fauci has a tremendous reputation as a fine manager of his Institute and the AIDS research program. But even the Washington Post in an editorial questioned whether your institute would be able to spend wisely the large influx of bioterrorism money proposed for your Institute in the President's budget. How has the Department responded to this type of criticism?

Mr. Allen: First, Dr. Fauci, the Director of NIAID, has extensive experience in managing a massive build up of resources as he so successfully did with the HIV/AIDS research program and he has used his experience to successfully ramp up the biodefense research efforts at NIH. Next, through the leadership of NIAID, and in close collaborations with outside experts, NIH developed a biodefense strategic plan and research agenda to develop countermeasures against bioterrorist threats. This strategic plan and the research agenda have already been endorsed by a Blue Ribbon Panel of experts and have already been implemented. The plan is sustainable over the long-term, supports and encourages the collaboration and the interest of industry, small businesses, academia and federal agencies in counter-bioterrorism research, and is responsive to the public health and national security needs. A central component of the plan is its focus on the translation of basic findings into products that can be used as effective countermeasures.

Mr. Regula: What steps has the Department taken to assure that hospitals, State and local health departments, and first responders are integrating their bioterrorism preparedness plans and systems? How will the Department monitor and valuate the extent of plan and systems integration?

Mr. Allen: In order for the States, cities and territories to receive the remaining 80 percent of the 2002 Emergency Supplemental funds for Bioterrorism Preparedness, they must submit work plans, which satisfactorily address critical benchmarks, and capacities, which have been defined in both the CDC and HRSA cooperative agreement guidelines. For example, HRSA's Hospital Preparedness Guidelines state, "The plan must address the roles of local, Tribal, Federal and military hospitals, referral centers, EMS systems, and outpatient facilities, as well as how they collaborate through such mechanisms as mutual aid agreements and regional or multistate consortia. The application should also demonstrate knowledge of bioterrorism preparedness resources on the local, regional, State and national level. Examples of resources include State and local emergency medical services, professional organizations, poison control centers, metropolitan medical response teams, disaster medical assistance teams, State and Federal emergency management agencies and other Federal programs such as CDC's Bioterrorism and Preparedness and Response Program and Division of Global Migration and Quarantine."

The CDC cooperative agreement includes numerous examples where the emphasis is placed on an integrated planning approach. For example, the Bioterrorism Advisory Committee should include representatives from: State and local health departments and government; Emergency Management Agencies; Emergency Medical Services; Office of Rural Health; Police, fire department and emergency rescue workers and occupational health workers; Community health centers; Red Cross and other voluntary organizations; and the hospital community (to include Veterans Affairs and military hospitals).

Another of the several critical capacities requires that "In collaboration with other federal agencies (e.g., Department of Health and Human Services, Health Resources Services Administration and the Office of Emergency Response, Federal Emergency Management Agency), assess readiness of hospitals and emergency medical services to respond to bioterrorism, other outbreaks of infectious disease, and other public health threats and emergencies, and include them in state/local plan development and exercises."

OFFICE OF EMERGENCY PREPAREDNESS

Mr. Regula: The Secretary has mobilized substantial resources within his Department to confront the bioterrorism threat. He created the OPHP late last year, headed by D.A. Henderson. Can you explain for us the different purpose of this Office compared to the already existing Office of Emergency Preparedness? Do you expect the OPHP to be temporary or permanent?

Mr. Allen: The Office of Emergency Preparedness (OEP) is an office created some years ago as the lead HHS agency as part of the Federal Response Plan. By design, OEP was created as the coordinating agency of the Department for Emergency Response and Preparedness for natural disasters and emergency consequence management, and to oversee the National Disaster Medical System. OPHP has a far broader function and responsibility of which OEP's activities are a small part. I created the OPHP last November to provide overall direction for all activities pertaining to public health preparedness. Thus, it is concerned with short and long-term policy, planning, research and execution.

A number of reports (e.g., SAIC and Gilmore Reports) specified that the HHS departmental approach was fragmented and inefficient and an office for oversight was recommended, resulting in the creation OPHP. The Office of Public Health Preparedness plays a critical role in ensuring that a one-Department approach to public health preparedness is taken, and that working relationships across Departments (e.g., DOJ, DOD, DEMA, EPA, etc.) and with Homeland Security are functional and maintained at all stages of planning and during emergency response. As there is no temporary solution to achieve Public Health Preparedness, OPHP is considered a permanent entity to ensure a unified approach.

ADVANCED RESEARCH IN BIOTERRORISM

Mr. Regula: I'm curious why the OPHP has a budget request for $5 million for "advanced research" in bioterrorism. Wouldn't NIH be the better place for this request due to its expertise, infrastructure, and grant apparatus?

Mr. Allen: Advanced Research funding is to support special projects throughout HHS's science agencies, not just work at NIH. In prior years, when the fund was administered jointly through ASPE and ASBTF, funding in this category laid the ground work for the major procurement of smallpox vaccine through the CDC and strengthened the science and technology base at FDA for its regulatory review of new bioterrorism-related vaccine candidates.

HEALTH PROFESSIONS PROGRAMS

Mr. Regula: Your FY03 budget request includes a large reduction for health professions training. But the account includes a new $60 million antibioterrorism program - educational incentives for curriculum development and training. The goal of this program may be laudable [to encourage interdisciplinary training to link health care providers and the public health infrastructure]. But isn't its creation shortsighted if one of the consequences is a nearly 50% cut in ongoing health professions programs?

Mr. Allen: The proposed reduction in funding for health professions programs was a separate decision from the proposed new focus on bioterrorism training. The health professions programs were established some decades ago to develop an adequate number and composition of health professions training programs. Today, the infrastructure has been established and graduates and enrollments fluctuate as the market demands. The President's Budget proposal reflects that continued funding is no longer needed.

At the same time, we do believe there is a need for a new focus to assure that the U.S. has a workforce of public health professionals that are equipped with the skills, knowledge and networks to recognize indications of a bioterrorist attack in their patients, appropriately treat these patients, and inform the public health system of such an event. Consequently, the President's Budget for FY 2003 proposes that funds be directed to this specific target area.

EPIDEMIC INTELLIGENCE SERVICE

Mr. Regula: As I understand it, the request proposes to place an EIS officer in every State. How many States currently have assigned EIS officers? What is the time-line for meeting this goal? What is the cost by fiscal year to reach the goal?

Mr. Allen: Following the events of September 11, 2001, the national demand for specially trained epidemiologists to address all-hazards emergency response increased. In FY 2002, CDC began a three year plan to place an EIS officer or, when necessary, an EIS-trained epidemiologist, in 50 states, 5 large cities, Washington, D.C., and Puerto Rico. Currently (as of May 2002), there are EIS officers in 25 states, plus Los Angeles and New York City.

During the past several months, the Epidemic Intelligence Service (EIS) program has aggressively recruited and selected 14 new officers for the 2002 class whose focus will be public health programs and activities related to emergency response -- most particularly bioterrorism. Additionally, twelve EIS-trained epidemiologists with the same program focus (i.e., emergency response and, especially, bioterrorism) will be assigned to eleven states and Washington, DC.

The Epidemiology Program Office/Centers for Disease Control and Prevention anticipates having an EIS Officer or an EIS trained epidemiologist in every state within three years prepared to provide technical assistance and response capabilities for all hazards emergencies.

EMERGENCY OPERATIONS CENTER

Mr. Regula: Please describe the current state of your Emergency Operations Center. How much of FY2002 funds were used to establish the Center. What are the plans for FY2003 and the associated costs?

Mr. Allen: CDC has maintained an Emergency Operations Center (EOC) as a part of its Emergency Preparedness and Response Program for many years. This EOC has been used to respond to large-scale natural disasters such as Hurricane Hugo and terrorist events such as the Oklahoma City Federal Building bombing. The EOC basic concept of operations has not changed to a great degree, but has grown in magnitude since the events of September 11th. CDC has always maintained a physical facility with the communications, information technology, and other equipment needed to mount a long term, sustainable public health response operation during emergencies. CDC has also maintained the technical expertise and staffing capabilities to provide emergency response expertise in a variety of fields such as health physics, toxicology, epidemiology, etc., during emergency events. What has changed is the magnitude and complexity of the operations. Given the growth and increase in CDC responsibilities and operational activities, CDC is currently establishing a new temporary EOC facility that can accommodate additional staff and support equipment.

Funding in FY 2002 to establish the temporary EOC will be approximately $4 million. This includes costs to design, equip, staff and to create the new "Standard Operating Procedures" and emergency protocols. The FY 2003 budget does not include specific proposals related to the EOC. More detailed plans are currently under development, but there is enough flexibility within the facilities budget to implement these plans once finalized.

LABORATORY REGISTRATION/SELECT AGENT TRANSFER PROGRAM

Mr. Regula: Please describe for the Committee the CDC's role and oversight of the national Laboratory Registration/Select Agent Transfer program. How much did the CDC spend on the program in FY2001 ? What are the estimates for FY2002 and FY2003? What is the select agent database? Does the CDC anticipate being given expanded responsibilities in this area? If so, have you developed estimates of the costs of implementing these new responsibilities?

Mr. Allen: The Antiterrorism and Effective Death Penalty Act of 1996 (Pub. L. 104-132) authorizes the Secretary of Health and Human Services (HHS) to regulate the transfer of certain biological agents (select agents) that have the potential to pose a severe threat to public health, and are of potential use by terrorists. The Centers for Disease Control and Prevention (CDC) is the agency within the Department responsible for promulgating this regulation. This regulation went into effect on April 15, 1997 and is designed to ensure that select agents are not shipped to parties within the United States who are not equipped to handle them appropriately, or who otherwise lack proper authorization for their requests. The facilities covered by Select Agent legislation include all governmental, academic, private and commercial laboratories. Of note, facilities are exempt by law from registering for the following reasons: (1) diagnostic and clinical labs, (2) CLIA labs, (3) work only with specific attenuated vaccines strains and (4) the use of toxins for medical purposes.

Currently, oversight of the Select Agent program resides within the External Activities Program, Office of Health and Safety, Office of the Director, Centers for Disease Control and Prevention.

CDC received $1 million in funding for select agents in FY 2001. Estimated expenditures of $4 million are expected in FY 2002. Estimates for FY 2003 are currently under review as a result of recent legislative changes, however, the current budget plan includes approximately $11 million for FY 2003.

Under 42 CFR 72.6 (Additional Requirements for Facilities Transferring or Receiving Select Agents), facilities wishing to transfer select agents are required to register with CDC and notify CDC of transfers. CDC is required to maintain a database of all facilities formerly and currently registered. The database includes, at a minimum, the name and address of the registered facility, the date the facility was registered, the facility's registration number, and the name and phone number of the responsible facility official. CDC also maintains data on shipments of select agents between registered facilities. This database is used for tracking interstate shipments of certain etiologic agents that could be used for bioterrorism purposes.

The current Select Agent legislation only governs facilities that transfer these agents. CDC anticipates that pending legislation will incorporate laboratories that possess and use select agents. The new regulation may increase the number of laboratory registrations from the current 324 to 1,500 or more. This change will also increase the number of inspections required.

While CDC is aware of discussions regarding an expanded role in this area, such plans are not yet finalized. If it is decided that CDC will take on new responsibilities, these will be funded with resources provided within the FY 2003 Budget request.

Mr. Regula: Please describe in greater detail the CDC's plans for tracking environmental and occupational contaminants in Manhattan.

Mr. Allen: It is expected that the last of the World Trade Center material will be removed from ground zero by June 11, 2002. CDC and ATSDR have been working very closely with the Environmental Protection Agency (EPA), Occupational Safety and Health Administration (OSHA), state environmental and health agencies, and New York City environmental and health agencies to assure that the appropriate environmental and occupational monitoring is being conducted. All of the monitoring results are being shared with the various agencies. CDC and ATSDR are actively reviewing the sampling results and advising what public health actions are appropriate. It is anticipated that the ambient environmental sampling will conclude after all of the material is removed from ground zero.

ATSDR is an active participant on the EPA Indoor Air Task Force. ATSDR has been advising EPA on how best to conduct the recently announced EPA/New York City cleaning and sampling program. Sampling results generated will reviewed by ATSDR.

In addition, all of the environmental and residential sampling results will be used by ATSDR and the New York City Department of Health during the development and implementation of the World Trade Center Disease Registry, a proposed central unified roster of exposed and potentially exposed persons. The registry would be used as the basis for health surveillance to evaluate short-term and long-term health effects related to the disaster and as a resource for future investigations and research studies.

The proposed registry would be implemented and managed by the New York City Department of Health, with technical and administrative assistance from ATSDR and CDC. The Federal Emergency Management Agency (FEMA) has proposed funding the start-up of the registry. ATSDR and CDC will assume operational costs associated with the registry in the outyears.

CDC is following up on long-term needs in New York through the following activities:

- Conducting health hazard evaluations to assess potential health effects from workers' exposure to dust in buildings near the recovery site.

- Providing technical assistance to the New York City Department of Health regarding the development of a voluntary registry of individuals who worked at, lived near, or responded to the World Trade Center attack.

- Working with local partners to develop a medical screening and monitoring program for workers involved in rescue and recovery operations at Ground Zero.

BIOTERRORISM

Mr. Regula: How many centers for strengthening bioterrorism and emergency preparedness did the CDC establish in FY2001 ? What was the cost of the Centers? How many centers does the CDC estimate will be supported in FY2002 and FY2003? What are the estimated costs? What are the goals of the centers program? How are they linked with academia?

Mr. Allen: In FY1999 and FY2000, CDC established a national system of Centers for Public Health Preparedness (CPHP) to strengthen state and local workforce capacity to protect against bioterrorism, other outbreaks of infectious diseases, and other public health threats and emergencies. This system currently includes three types of Centers: 1) Academic or "base" Centers linking Schools of Public Health with state, local and regional health professionals, 2) Specialty Centers at universities addressing unique areas of preparedness, such as public health law, and 3) Local Exemplar Sites at city-county health departments developing advanced applications in community mobilization, communications/information dissemination, and workforce training. This system leverages the "best practices" of front-line practitioners and fosters the development of practical, competency-based courses and materials, based on innovative approaches to preparedness and response.

There are currently 14 Centers: 7 Academic Centers, 4 Speciality Centers, and 3 Local Exemplar Sites. Three of the Academic Centers were established in FY2001 with partial planning grants, and one new Speciality Center was added through a direct Congressional appropriation. The total extramural awards to all Centers in FY2001 was approximately $6.5 million. The locations of the 14 Centers is as follows:

Academic Centers

- Columbia University Mailman School of Public Health, New York, NY
- University of Illinois at Chicago School of Public Health, Chicago, IL
- University of North Carolina - Chapel Hill School of Public Health, Chapel Hill, NC
- University of Washington School of Public Health and Community Medicine, Seattle, WA
- University of Iowa College of Public Health, Iowa City, IA (FY01 - Partial Planning Grant)
- University of South Florida College of Public Health, Tampa, FL (FY01 - Partial Planning Grant)
- Saint Louis University School of Public Health, St. Louis, MO (FY01 - Partial Planning Grant)

Specialty Centers

- Dartmouth College Medical School Interactive Media Laboratory, Hanover, NH
- Saint Louis University Center for Study of Bioterrorism & Emerging Infections, St. Louis, MO
- Johns Hopkins Bloomberg School of Public Health & Georgetown University Law Center: Center for Law and the Public's Health, Baltimore, MD
- University of Findlay National Center of Excellence for Environmental Management, Findlay, OH (FY01)

Local Exemplar Sites

- DeKalb County Health Department, Decatur, GA
- Denver Health, Denver, CO
- Monroe County Health Department, Rochester, NY

In FY2002, $20 million will be made available to fund eight additional Academic Centers and four new Academic Centers will be established via competitive grant among the remaining 16 Schools of Public Health. The locations of the eight approved Centers are as follows:

- Emory University, Rollins School of Public Health, Atlanta, GA
- Harvard University School of Public Health, Boston, MA
- Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
- University at Albany SUNY, School of Public Health, Albany, NY
- Tulane University School of Public Health and Tropical Medicine, New Orleans, LA
- University of California at Los Angeles School of Public Health, Los Angeles, CA
- University of Minnesota School of Public Health, Minneapolis, MN
- University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA

The remaining 16 Schools of Public Health are:

- Boston University School of Public Health, Boston, MA
- Loma Linda University School of Public Health, Loma Linda, CA
- Texas A&M School of Rural Public Health, Bryan, TX
- University of California at Berkeley School of Public Health, Berkeley, CA
- George Washington University School of Public Health & Health Services, Wash DC
- Ohio State University School of Public Health, Columbus, OH
- San Diego State University Graduate School of Public Health, San Diego, CA
- University of Alabama at Birmingham School of Public Health, Birmingham, AL
- University of Massachusetts School of Public Health and Health Sciences, Amherst, MA
- University of Michigan School of Public Health, Ann Arbor, MI
- University of South Carolina The Norman J. Arnold School of Public Health, Columbia, SC
- University of Texas School of Public Health, Houston, TX
- Yale University School of Public Health, Princeton, NY
- University of Medicine and Dentistry of New Jersey-School of Public Health, Piscataway, NJ
- University of Oklahoma College of Public Health, Oklahoma City, OK
- University of Puerto Rico School of Public Health, San Juan, PR

Over the past two years, the Academic Centers have closely collaborated and shared resources in the development and delivery of their programs and services for bioterrorism preparedness and response. Using a common framework developed in partnership with national public health organizations, the Centers focus on such topics as: critical bioterrorism agents, surveillance and epidemiology, incident command, health/risk communication, and legal authorities. Since inception, the Centers, in collaboration with their state and local partners, have prepared more than 180 educational products; trained more than 200,000 public health and health care professionals; and developed an inventory of faculty expertise and assets available for local, regional, and national emergencies. Following the events of September 11th and the anthrax exposures, the CPHPs more than doubled their goals for outreach.

In FY2002, the Academic Centers will be located in 17 states; each Center will receive $1 million. each. No additional funding is requested in the President's 2003 budget for additional centers to ensure nationwide coverage. Specialty Centers complement the activities of the comprehensive Academic Centers and may be located in Schools of Public Health, Medicine, Nursing, Law, or other accredited institutions of higher learning.

There are three Local Exemplar Sites currently funded in local health departments. These Sites serve as Advanced Practice Centers for frontline public health at the community level. It is anticipated that two additional sites will be funded in 2002 and by 2003, there may be one Center in each of 10 regions. Current funding for the existing three Exemplar Sites is $1.8 million. It is estimated that $500,000 will be awarded to each new Center, for an additional $3,500,000. All Advanced Practice Centers are linked with academic institutions.

RAPID TOXIC SCREEN

Mr. Regula: Please describe the significance and cost to add 30 chemicals to the Rapid Toxic Screen. How many laboratories in the United States have this capability?

Mr. Allen: The Rapid Toxic Screen is a panel of tests that measures chemical agents in blood and urine samples to determine in an attack what chemical agent (or agents) has been used, who has been exposed, and how much exposure each person has had. This exposure information will help guide public health management decisions for populations as well as medical decisions on individual patient management. Measurements in the Rapid Toxic Screen are analytically extremely challenging requiring state-of-the-art approaches and research to develop new techniques -- almost always utilizing isotope dilution mass spectrometry. Measurements must also simultaneously be analytically sensitive, specific, accurate, precise, rapid, and be able to measure multiple chemical agents in small volumes of blood or urine. In addition, metabolism studies must be done on at least two species of animals to determine how the chemical agents change once in the body so that the analytical method targets the correct form of the chemical agent in blood and/or urine.

At least hundreds of chemical agents have potential for use by terrorists. Prioritizing these chemical agents for inclusion in the Rapid Toxic Screen is based on intelligence information (including information on agents that have been weaponized), availability of the chemical agent to a terrorist, acute and chronic toxicity of the agent, and the ability of a terrorist to expose persons to the agent through air, water, dust/soil and food.

Based on these criteria, we would consider adding 30 chemicals to the Rapid Toxic screen to be of high public health significance. The cost to cover animal research to assess metabolism of the chemical agents, analytical chemistry research and method development, and validation studies is dependent on the particular chemicals chosen but can be estimated at about $14-15 million dollars.

CDC is working with five state laboratories to transfer methods in the Rapid Toxic Screen. So far, these laboratories have received analytical methods for the major nerve agents (including sarin gas that was used in Japan in 1995, soman, tabun and VX) and the sulfur mustard agents (generally known as the blistering agents). They are in the process of receiving methods for cyanide based compounds and lewisites. Outside of

CDC and these five state labs, there are no labs that currently have available measurements of a broad panel of chemical agents as is done in the Rapid Toxic Screen. CDC is discussing the Rapid Toxic Screen methods with other Federal laboratories, including DOD and the FBI.

A major priority for CDC is to research analytical techniques to simplify measurements in the Rapid Toxic Screen so they will not require such advanced analytical instrumentation and techniques and can be more easily transferred to other labs, especially state and local public health laboratories.

FUNDING FOR UPGRADING CDC CAPACITY

Mr. Regula: Please provide the Committee with a table itemizing funding for Upgrading CDC Capacity for Fiscal Years 2001, 2002 and 2003.

Mr. Allen: The table is below:

Centers for Disease Control and Prevention
Funding for Upgrading CDC Capacity -- FY 2001 - FY 2003
(Dollars in Millions)

	FY 2001 Approp.	FY 2002 Estimate	FY 2003 Estimate **
Upgrading CDC Capacity:			
-- Select Agents	$1.0	$4.2	----
-- State/Local Technical Assistance & Oversight	----	$4.2	----
-- Preparedness & Response	$9.2	$61.9	----
-- Laboratory Capacity	$16.4	$37.2	----
-- Surveillance & Epidemiology	$4.0	$14.0	----
-- Research	$1.1	$13.3	----
-- Anti-Infective Agents *	----	$2.0	----
Subtotal, CDC Capacity -	**$31.7**	**$136.7**	**$158.7**

* In FY 2001, Anti-Infective Agents was funded from a different budget category ($2.0M).

** A final distribution by category has not been finalized at this time. A comprehensive review of requirements is currently being conducted. Funding in FY 2003 for each category will be representative of the need and priorities of the Administration.

BIOTERRORISM PREPAREDNESS

Mr. Regula: Please describe for the Committee Phase 1 of the national training plan for bioterrorism preparedness. What does the plan involve for phases 2 and 3 and what is the implementation timeline?

Mr. Allen: The National Collaborative Training Plan for Bioterrorism Preparedness is a critical building block of CDC's strategic plan for Bioterrorism Preparedness and Response. The plan originally outlined training required by CDC personnel to implement the Agency's event response operational plan (Phase 1) and strategies for training public health and medical facility personnel in collaboration with partners (Phase 2). In addition, the need to incorporate bioterrorism preparedness, response and recovery competencies into an overall national workforce development initiative for frontline public health professionals in State and local agencies was addressed (Phase 3).

The events of September 11th and the anthrax outbreaks last fall have greatly accelerated the original time line and influenced the content and focus on target audiences. Now rather than a phased approach, CDC is simultaneously working on training for both internal staff and front line public health. Following September 11th, CDC staff who would be deployed to the field were trained as Emergency Response teams; State, local, federal partners and CDC staff have also received training on smallpox guidelines and response planning. CDC's training plan activities are currently focused on: (1) working with state and local agencies to support critical and enhanced capacities as outlined in CDC FY2002 Supplemental Funds for Program Announcement 99051, Public Health Preparedness and Response for Bioterrorism (specifically Focus Area G, A, and F); (2) expanding the Centers for Public Health Preparedness program which links academic assets with state and local needs; 3) working with the National Association of County and City Health Officials (NACCHO) and the Association of State and Territorial Health Officers (ASTHO) to effectively reach public health practitioners in state and local health departments; (4) fostering partnerships with a broad array of organizations (academic, professional associations, federal, state and local partners) to implement strategies to prepare public health, medical staff, first-responders and volunteers and (5) collaborating with Association of American Medical Colleges on their bioterrorism initiative for medical students, residents and practicing physicians entitled "First Contact, First Response. " In concordance with the plan, CDC developed and disseminated the CDC Responds series which has reached over 1.6 million public health and health care viewers. This satellite broadcast series encompasses a broad range of topics on aspects of bioterrorism preparedness and response. The National Laboratory Training Network continues to provide distance learning, self-instruction and wet-lab courses on bioterrorism for laboratorians and disseminated multimedia training packages to 4200 Level A laboratories.

VACCINE HEALTHCARE CENTER

Mr. Regula: What is involved in being designated a vaccine healthcare center? How will the sites be selected? What is the timeline for establishment of the network of VHC's? What are the estimated costs for FY2002 and FY2003 for the network? Will the NIH also provide financial support to the network? What is involved in being designated a vaccine healthcare center? How will the sites be selected?

Mr. Allen: The Vaccine Healthcare Center (VHC) Network is the result of a partnership between CDC and DoD to develop a DoD-wide network of regional centers of excellence to address vaccine-related healthcare needs and support continuous quality improvement of immunization healthcare delivery, education, research and case management of complex vaccine adverse events for DoD beneficiaries. The lead VHC is at the Walter Reed Army Medical Center (WRAMC). The WRAMC VHC is also the first regional VHC. The open house ceremony for the VHC Network was held at the WRAMC VHC on September 6, 2001 and the VHC Network will eventually include centers on Army, Navy, and Air Force facilities within the continental U.S. and potentially on facilities outside the continental U.S.

Each VHC will have a Regional Director, clinical staff, research staff, and administrative support staff. These VHC staff will typically be non-military contract personnel dedicated solely to the VHC mission and work. Current and future VHCs are or will be located on military bases and linked to base healthcare operations.

The Lead VHC at WRAMC, with the assistance of DoD Health Affairs and CDC, will recruit and identify additional VHC sites, assist with hiring and training personnel, provide leadership and guidance to the VHC Network clinical and research mission and objectives, and coordinate Network operations and reporting.

Mr. Regula: What is the timeline for establishment of the network of VHC's?

Mr. Allen: It is projected that two to three regional VHCs will be added to the Network each year for the next five years. Depending on the eventual need, it is projected that the total number of VHCs in the Network will be between 10 and 15.

Mr. Regula: What are the estimated costs for FY2002 and FY2003 for the network?

Mr. Allen: Infrastructure costs associated with the start-up of future VHC sites will be the responsibility of DoD and are estimated to be about $400,000 per site. Training costs for staff at each VHC will be shared by CDC and DoD and are estimated to be about $50,000 per site. CDC will support VHC costs associated with enhancing anthrax vaccine safety and conducting vaccine safety studies and observational research, which is projected to cost about $400,000 per site per year. DoD will support VHC costs associated with clinical operations, case management, and assuring continued quality improvement of vaccine delivery within DoD, which is projected to cost about $500,000 per site per year.

The CDC costs for the Network will be $1.6 million in FY 2002 and an estimated $2.4 million in FY 2003. The estimated DoD costs for the Network will be $3.0 million in FY 2002 and $4.0 million in FY 2003.

Mr. Regula: Will the NIH also provide financial support to the network?

Mr. Allen: No.

PHARMACEUTICAL STOCKPILE

Mr. Regula: How many Push Packages does the CDC plan to add to the pharmaceutical stockpile in FY2002? How much does the CDC estimate will be expended in FY2002 and FY2003 to aid states and territories in planning for the effective management and use of NPS assets?

Mr. Allen: CDC has increased the number of Push Packages from 8 to 12 in FY2002. Sixty-five million dollars in FY2002 is estimated to be expended for 62 project areas including all states, Chicago, DC, LA, NYC, plus 8 U.S. Territories for infrastructures at various levels to manage and use deployed pharmaceuticals.

Mr. Regula: How will the CDC assure that State disease reporting systems will provide data in compatible formats for CDC to assemble and analyze?

Mr. Allen: CDC is developing detailed specifications as part of the National Electronic Disease Surveillance System (NEDSS) for the format in which data are to be provided from states to CDC, so that these data can be assembled and analyzed for the country. States can use either a state NEDSS solution or the NEDSS Base System to send these data as an electronic message. The guidance provided the states for investment of the federal preparedness funding requires states to use these standard messages.

Mr. Regula: What is the short-term goal for enhancing the preparedness of biological and chemical laboratories? What are the elements of measuring and/or enhancing laboratory capacity? Where is the greatest need?

Mr. Allen: Biological laboratories: Focus Area C of the Supplemental Funds (biological laboratory capacity) will award $142 million to state and local health departments for upgrading laboratory capacity. The short term goal is to provide for surge capacity, increased staffing needs and laboratory testing capabilities for all of the Category A agents. These three areas are those with the greatest needs. The cooperative agreement includes benchmarks for these areas that the state and local health agencies must meet.

Chemical laboratories: The short-term goal for enhancing the preparedness of chemical laboratories is to enable them to develop and use high quality, rapid and interpretable laboratory tests to measure chemical agents in blood or urine samples in order to determine what chemical agent (or agents) has been used during an attack, who has been exposed, and how much exposure each person has had. CDC has developed methods for measuring chemical agents in blood and urine and continues to expand this research area. CDC is working to enhance laboratory capacity at the state level by funding expanded laboratory capability and transferring methods to five state public

health laboratories (i.e., New York, Virginia, California, Michigan, and New Mexico). So far, these laboratories have received analytical methods for the major nerve agents (including sarin gas that was used in Japan in 1995, soman, tabun and VX) and the sulfur mustard agents (generally known as the blistering agents). They are in the process of receiving methods for cyanide based compounds and lewisites (see also answer to R. 13). The greatest need in enhancing preparedness of chemical laboratories is in funding the research required to develop high quality, rapid, and interpretable methods to measure chemical agents in blood and urine. This research is a pre-requisite to having methods that can be transferred to state laboratories.

CDC'S LABORATORY PREPAREDNESS

Mr. Regula: What is the greatest need in terms of CDC's laboratory preparedness? What lessons did you learn regarding laboratory preparedness and response in the wake of September 11th and the anthrax exposures?

Mr. Allen: CDC's greatest needs for an appropriate biological laboratory response would be the trained staff, facility and resource infrastructure to support extended 24/7 response capacity for high throughput testing of samples and specimens. Many of the critical agents for biological terrorism had been eliminated or seen very infrequently, so most of today's laboratorians are not skilled in the detection of these agents, thereby creating a very limited supply of staff. For critical surge capacity response, additional equipped laboratories with appropriate safety precautions are necessary.

Experience with the anthrax events of 2001 has exposed shortfalls in CDC's laboratory preparedness for bioterrorism. Significant gaps still exist in the following areas: (1) laboratory staffing; (2) laboratory swing space for outbreak surge response; (3) rapid diagnostic capability, including equipment and supplies; (4) an integrated specimen management and tracking system; (5) research and development to include assay development and validation; and (6) new laboratory capacity and protocols for environmental testing. These gaps will be addressed with the approximately $37 million in funding to enhance laboratory capacity in FY 2002.

Mr. Regula: How much will be used in FY2002 to enhance CDC's laboratory capacity? What is your estimate for FY2003? How will the FY2003 funds be used?

Mr. Allen: In FY2002, CDC is estimated to spend $37,166,000 total to enhance both CDC's chemical and biological laboratory capacity. Level funding is anticipated in FY2003.

Mr. Regula: How much is requested for FY2003 for enhancing biological laboratory capacity? How much is requested for FY2003 for enhancing the capacity of chemical laboratories?

Mr. Allen: CDC is currently conducting a comprehensive budget review of requirements in the FY 2002 bioterrorism budget. Based on this review, a final distribution of spending figures by budget category for FY 2003 will be provided. Current preliminary estimates suggest that FY 2003 funding for enhancing biological and chemical capacity may include approximately $20 million and $17 million respectively.

Mr. Regula: What is the CDC's involvement in research involving anthrax? How do you distinguish between research on an anthrax vaccine conducted by CDC and research conducted by NIH? How, and to what extent, is the DOD involved with you in research on anthrax? What research, if any, is CDC involved in as a result of providing antibiotics to the thousands of individuals who were potentially exposed to anthrax last fall?

Mr. Allen: CDC is doing research on a number of aspects of anthrax related to public health response. Areas of active CDC research include epidemiologic investigation, surveillance, diagnosis, treatment, post-exposure prophylaxis and other prevention strategies, and environmental assessment and remediation. The anthrax vaccine research conducted by CDC is focused on studies of the currently licensed anthrax vaccine to make it better tolerated (switching from giving the vaccine just under the skin to giving it in the muscle) and more useful (by reducing the 6 dose 18-month regimen to as few as 3 doses over 6 months) and identification of blood tests to demonstrate when someone is protected (often called "immunologic correlates for protection") following anthrax vaccination.

The anthrax vaccine research conducted by NIH is focused on development of a new anthrax vaccine. The CDC and NIH efforts on anthrax vaccines are highly complementary, and CDC will provide laboratory support for the NIH effort to develop a new anthrax vaccine. CDC is working in close collaboration with DoD on its anthrax vaccine research efforts; this includes surveillance efforts to evaluate adverse events in military populations, design and conduct of human studies in civilian groups, and conduct of studies in animals. CDC is carefully monitoring the health status (at 10 days, 30 days, 60 days, and then 6, 12 and 24 months) of the approximately 10,000 persons who were recommended to take 60 days of antibiotics; these studies are providing critical information about efficacy of post-exposure treatment for prevention of anthrax, occurrence of adverse events associated with long-term antibiotic use, and adherence to the recommended duration of therapy.

EMERGING INFECTIOUS DISEASE AGENTS

Mr. Regula: Is the CDC involved in research and development of better diagnostics for emerging infectious disease agents? If so, what do you estimate you will spend in FY2002 and FY2003 in this area? Is this predominately intramural or extramural research?

Mr. Allen: One of the activities that CDC is recognized for is the development of diagnostic assays for emerging infectious disease agents. These include rapid assays that are more sensitive and specific than traditional assays. In addition, a new program has begun developing assays that will help identify new agents, as was done for detection of the West Nile Virus. CDC has continually been involved in enhancing diagnostic capabilities for new and re-emerging infectious diseases. A specific spending figure for diagnostic assay testing/development is not tracked.

Mr. Regula: Is any of the bioterrorism research money awarded extramurally? If so, how much?

Mr. Allen: CDC will award bioterrorism research money extramurally. Currently, CDC is conducting a comprehensive budget review and spending approval process of requirements for all bioterroism programs. A final funding level for extramural research is not available at this time.

HEALTH ALERT NETWORK

Mr. Regula: What are the components of the Health Alert Network? Does it simply involve providing the hardware for connecting State and local health departments?

Mr. Allen: The Health Alert Network (HAN) is a nationwide, integrated information and communications system serving as a platform for a variety of activities, such as distribution of health alerts, dissemination of prevention guidelines, distance learning, national disease surveillance, and electronic laboratory reporting. HAN also provides a foundation for CDC's bioterrorism and related initiatives to strengthen preparedness at the local and state levels. In its first phase, which does have a hardware component, the HAN initiative focused on building an information and communications infrastructure for the public health system. The value of this phase of networking was demonstrated clearly after September 11th and during the anthrax attack. As the initiative enters its second phase, the focus broadens to include building excellent local health agencies by improving the information and knowledge base for public health practice and by enhancing capacity and performance of local public health agencies broadly.

Mr. Regula: What is your goal for connectivity with State and local health departments? What is the current estimate of connectivity of State and local offices?

Mr. Allen: Connectivity is an integral component of the FY 2002 Supplemental Funds for Public Health Preparedness and Response for Bioterrorism, which is the large state bioterrorism grant awarded early this year. Critical benchmarks 11 and 12 specifically address required elements for connectivity. States are expected to have 90% of their population covered by the Health Alert Network by August 2003. In order to meet this critical benchmark, the state health department should have connectivity to all

local health departments/jurisdictions in addition to hospitals and other emergency response agencies. The ultimate goal is 100% of the U.S. population be served by a local public health jurisdiction connected to the Health Alert Network; often, the local jurisdiction is a county health department.

Currently, 68% of all counties have continuous, high-speed Internet connectivity. Most local health agencies (67%) have a system for sending urgent health alerts to targeted community groups. Under the supplemental grant guidance, states must establish a method for 24/7 flow of information to local health officials, hospital emergency rooms, and law enforcement officials. Seventy percent of local health jurisdictions currently have the capacity for round-the-clock operability.

Mr. Regula: How will you integrate the funds previously awarded under the Health Alert Network with the nearly $1 billion provided to States to upgrade State and local health department capacity?

Mr. Allen: The Health Alert Network was designed to:

- establish infrastructure for information, communications and training at the local, state and national level (including internet connectivity, broadcast capability, and distance learning infrastructure)
- establish linkages between public health agencies and community partners, including hospitals and other partners
- improve knowledge management for frontline public health (including reference images, information, practice guidelines, protocols, profiles of state and local health departments and labs that include locator information for key staff, and training and education programs)
- establish a set of exemplar sites for advanced public health practice (to function as centers ofinnovation, to partner with and assist peer communities, and as testing sites for national programs)

The requirements for establishing the computer-based infrastructure of the Health Alert Network is included in Focus Area E of the larger BT grant program. Focus Area E covers the Health Alert Network, in addition to communications and other information technology requirements. By integrating these parts of the program, we will be able to ensure that all information technology investments meet the same technical standards. Advancing the functional uses of the Health Alert Network is addressed, in part, in other areas of the grant program. For example, the internet connectivity specifications required for the Health Alert Network that will enable grantees to expand their internet-based learning capacity is addressed in Focus Area G. Expanding the Health Alert Network to all parts of the public health system and appropriate community partners will enhance the ability of public health agencies to communicate (covered in Focus Area F) and conduct surveillance (under Focus Area B).

Some of the functional aspects of HAN are being addressed with FY 2002 funding, similar to the amount provided in FY 2001. These funds will focus on addressing local needs (85% of fund must go to the local level), alternate communication methods when computers and phone lines fail or become overloaded, distance learning coordination and infrastructure, and other uses of HAN. Future allocations will address other needs, including mapping of the national, state, and local network as a critical infrastructure asset; development and dissemination of information, guidelines, best practices, and training for improving local public health practice; and tools for emergency simulations, secure data gathering and other needs.

CDC NATIONAL PHARMACEUTICAL STOCKPILE

Mr. Regula: I understand that one of the issues identified last fall was the importance of State and local health officials having a plan for the distribution of PUSH packs in their communities. How do you plan to assure communities have distribution plans in place?

Mr. Allen: The CDC Guidance for FY 2002 Supplemental Funds for Public Health Preparedness and Response for Bioterrorism includes critical capacities or core expertise and infrastructure targeted for immediate implementation in states and local communities. Critical capacity 3C under Focus Area A in the Guidance requires states to effectively manage the CDC National Pharmaceutical Stockpile (NPS) should it be deployed-- translating NPS plans into firm preparations, periodic testing of NPS preparedness, and periodic training for entities and individuals that are part of NPS preparedness. Distribution of the PUSH packs is a large part of this training program. States were provided with $65 million to meet this requirement.

Further, CDC has developed the NPS Training Education and Demonstration (TED) package to be used to assist in the preparation and training of state and local health departments and responders in the proper receipt and distribution of the NPS assets. NPS TED will be used as part of the NPS hands on training conducted at the Office of Emergency Preparedness' Noble Training Center located at the old Fort McClellan base in Anniston, Alabama or in field exercises.

SMALLPOX VACCINE

Mr. Regula: What is the impact of the recent donation of 70 million doses of the smallpox vaccine on the Department's smallpox vaccine plans? When do you estimate the Government will reach the goal of having sufficient doses on hand to immunize the entire population if necessary?

Mr. Allen: The goal of a smallpox vaccine stockpile is the availability of a dose of smallpox vaccine for every American. Currently, 15.4 million doses of existing smallpox vaccine from Wyeth can be diluted to cover 75 million individuals, based on

the results of the recent NIH study. This, plus the new 54 million doses from Acambis and 155 million doses from Acambis-Baxter, will provide sufficient vaccine for "every American" by the end of calendar year 2002.

The recently donated 70 million doses of Aventis Pasteur vaccine will not change these plans to purchase additional vaccine. The Aventis vaccine, which will eventually will need to be replaced in the stockpile with a modern cell culture vaccine that meets current regulatory standards, should be thought of as an "insurance policy" until new vaccines are ready.

Mr. Regula: Once in hand, what do you plan to recommend concerning the vaccination of Americans against smallpox?

Mr. Allen: The risk for smallpox occurring as a result of a deliberate release by terrorists is not known, but considered very low. Nonetheless, HHS began undertaking efforts in November 2001 to stockpile as much vaccine as needed to protect the nation in the event of an outbreak of smallpox. Production of new vaccine is underway, and, once completed, will bring the total number of vaccine doses in the nation's stockpile to 286 million by the end of this year, enough to protect every United States citizen, if needed.

This recent effort to build sufficient stores of smallpox vaccine has generated national dialogue on the current recommendations for use of smallpox vaccine. As part of this ongoing dialogue, the Advisory Committee on Immunization Practices (ACIP) will begin reviewing its existing recommendations for smallpox vaccination.

Currently, smallpox vaccination is not recommended for the general public because it can cause serious complications, even death. Vaccination is indicated only for laboratory workers directly involved with vaccinia virus or closely related orthopox viruses (for example, monkeypox). Health care workers who may have contact with these viruses through clinical trials for vaccines but whose contact with these viruses is limited to contaminated materials (for example, dressings) are at a lower risk of inadvertent infection than laboratory workers, but may be considered for vaccination.

A joint Advisory Committee on Immunization Practices (ACIP) and National Vaccine Advisory Committee (NVAC) met in Atlanta, May 8 & 9, to begin reviewing existing recommendations for smallpox vaccination and formulating recommendation options to be presented to the full ACIP. Some of the issues the working group considered in their review of current policy for smallpox vaccination include:

- With no known cases of smallpox worldwide, should routine smallpox vaccination be resumed in the United States?

- Should recommendations for the use of vaccine be dependent or modified based on the available supply of smallpox vaccine?

- Should public health and medical personnel identified as early responders to a possible smallpox case or attack be vaccinated prior to such an event?

- If responders to a smallpox event should be vaccinated prior to an event, what guidelines should be established to determine which responders to vaccinate?

- Should the current recommendation for "ring" vaccinations as the strategy of choice for the control of smallpox in the event of an attack be modified?

The working group will present options and the pros and cons for each option at the regularly scheduled ACIP meeting to be held on June 19-20, 2002 in Atlanta. At that time, ACIP will review and consider the recommendation options and other information obtained from the scientific community, stakeholders and the general public for the use of smallpox vaccine. The ACIP will then work to finalize recommendation's for use of smallpox vaccine in the United States. The recommendations will then be forwarded to the Secretary, Health and Human Services for review.

One major step in this process will be gathering public and stakeholder input into the decision making process. Therefore, CDC is planning a series of meetings between now and June 19 to gather public and stakeholder comment. There will be four public forums (New York and San Francisco, June 6 and St. Louis and San Antonio, June 8), a stakeholders meeting in Atlanta on May 30, and a scientific meeting at he National Academy of Sciences (date to be determined). CDC will also take comment through its web site, www.cdc.gov/nip. This site is being developed now and will be operational soon.

FORT COLLINS FACILITY

Mr. Regula: Within the funds requested for bioterrorism buildings and facilities, how much is requested for the Ft. Collins facility? What is the construction timeline for design and construction of the facility? Have decisions been made regarding the size of the new facility? How does this compare to the existing facility? Do you expect the new laboratory to have expanded responsibilities? Could it be used to meet some of CDC's future surge capacity requirements? Within the funds requested for bioterrorism buildings and facilities, how much is requested for the Ft. Collins facility?

Mr. Allen: CDC does not have a formal cost estimate at this time because we still need to go through architectural programming and negotiate the site acquisition, utilities and security package.

Mr. Regula: What is the construction timeline for the design and construction of the facility? Have decisions been made regarding the size of the new facility? How does it compare to the existing facility?

Mr. Allen: The architectural programming will be underway by the end of May 2002. The programming effort will determine the size and composition of the new facility. The new facility will be larger than the existing facility. CDC plans to produce a detailed project budget and implementation schedule by September 2002, that will provide the milestone design and construction dates for the project. CDC will make every effort to have the new facility ready for occupancy by 2007 – the expiration date of the existing lease.

Mr. Regula: Do you expect the new laboratory to have expanded responsibilities? Could it be used to meet some of CDC's future surge capacity requirements?

Mr. Allen: The replacement facility for the Division of Vector-Borne Infectious Diseases (DVBID) in Fort Collins will provide CDC with enhanced capacity to augment the Department's bioterrorism efforts. DVBID is responsible for two of the six category A bioterrorism agents (plague and tularemia) and an important category B agent (Venezuelan equine encephalitis). DVBID staff are experienced and prepared for BT events. Therefore, in addition to supporting national efforts with any activities related to these agents, DVBID/Fort Collins will be poised to provide surge capacity in laboratory, epidemiologic and response efforts, at a site remote from Atlanta. Vector-borne diseases have become among the most important emerging infectious diseases of the 21st century. The laboratory must accommodate future needs in this area also.

Mr. Regula: What will the balance of the bioterrorism buildings and facilities request be used for in FY2003?

Mr. Allen: If the balance of the $100 million FY2003 funding is not be needed for the Ft. Collins Replacement Lab Project, this funding may partially fund the initial design of the laboratory components of the East Campus Consolidated Lab Project, Edward R. Roybal Campus, Atlanta.

BIOTERRORISM

Mr. Regula: Do you expect the NIH bioterrorism budget to remain at levels comparable to the $1.7 billion FY03 request for the next five years or so?

Mr. Allen: Our bioterrorism research effort will continue to be a major component of our Nation's readiness efforts. Besides supporting research in areas of the highest priority, we will also start to build the specialized research infrastructure that is needed to conduct research on these highly dangerous pathogens.

Our focus in the next few years will be on: expanding the number and capacity of our extramural centers for excellence for biodefense and emerging infections; expanding training; and expanding basic and pre-clinical research as the new specialized research facilities come on line. We will also concentrate on expanding our clinical trials

infrastructure to support and conduct a much larger number of clinical trials, including Phase III trials, of candidate vaccines and drugs. The FY 2003 request for NIH also includes some expenditures to build specialized research infrastructure. However, as the nation's specialized research capacity increases, we will shift the funds from building research infrastructure to supporting and conducting the broader range of research that is needed, and in which the new specialized research facilities are designed to support. The NIH bioterrorism research agenda will receive full consideration during the review and decision-making process in constructing the FY 2004 and future year budgets.

Mr. Regula: In FY03, the bioterrorism research request is almost entirely within the NIAID budget. In future years, do you expect the other NIH institutes to increase their share of the bioterrorism research request?

Dr. Fauci: While the President's request for FY03 biodefense research spending is, indeed, almost entirely within the NIAID budget, money will be transferred from NIAID to other NIH Institutes to support research projects that are relevant to the overall NIH Biodefense Research Agenda but within the purview of those other Institutes or Centers. For example, NIAID has already initiated discussion on possible collaborations with a number of other Institutes including the National Institute of Mental Health, the National Institute of Child Health and Human Development, the National Institute on Aging, and the National Institute of Bioengineering and Bioimaging. NIAID has also developed a program under which intramural scientists of Institutes other than NIAID can apply for funding to support research relevant to the NIH Biodefense Research Agenda.

In short, the NIH will support a comprehensive research and development program that is responsive to the scientific priorities articulated in the NIH Biodefense Research Agenda. The specific components of this program will be coordinated by the NIAID but carried out in the intramural and extramural programs of a number of relevant Institutes.

Mr. Regula: How much of the $977M of the FY03 bioterrorism research budget is expected to have out-year commitments?

Dr. Fauci: All of the $977M is funding programs with out-year commitments.

Mr. Regula: Dr. Fauci, I notice you don't ask for extended availability of the bioterrorism money. Are you confident you can obligate all of it by September 30, 2003?

Dr. Fauci: We feel confident that the money will be obligated by 30 September 2003 and that the money will be well spent. In this regard, we have built a long-range strategic plan and research agenda that is aimed at quickly engaging and supporting the collaboration and interest of industry, academia and federal agencies in biodefense

research, and is responsive to the public health and national security needs. A Blue Ribbon Panel of experts has already endorsed the strategic plan and research agenda, and the plan and agenda are already being implemented.

Mr. Regula: You also request $283 million for hospital infrastructure. These funds are designated for expanding lab capacity, infection control, and purchasing protective equipment. What formula would you use to distribute these funds to State health departments? Have you identified particular program areas of greatest need? How many hospitals do you expect to be assisted?

Dr. Duke: The method for distributing funds is still under discussion. Our intention is to allow the individual States to determine what is most important for their jurisdiction among the three designated program areas: hospital laboratory capacity, infection control and decontamination facilities and/or equipment. We would expect multiple hospitals to be involved in each State.

Mr. Regula: $19 million of your bioterrorism budget is designated for the ongoing emergency medical services for children (EMSC) program. This program has been funded for many years through the regular HRSA appropriation. Does the proposal to fund it in FY03 from the Public Health and Social Services Emergency Fund as "bioterrorism" indicate any intended change in the nature of the program?

Dr. Duke: The program would have an expanded emphasis on linking to the broader emergency preparedness effort. The EMSC was created to support the Trauma/EMS programs in the States to respond to the special needs of children. Although substantial progress has been made over the last 17 years, much still needs to be accomplished to assure that children's unique health needs are met. The EMSC program has been proactive in taking steps to meet the special needs of children in disaster and bioterrorism events. On September 12, less than 24 hours after the plane crashes in New York, Virginia and Pennsylvania, the program created and distributed via the internet a special publication addressing the special needs of children after a disaster. Further, the EMSC program has issued a supplemental grant award for the development of a color coding schema for special medication doses of most commonly used antibiotics for biological agents used in terrorism.

POISON CONTROL CENTERS PROGRAM

Mr. Regula: The same question applies to the $21 million poison control centers (PCC) program. Does its designation as "bioterrorism" under the emergency fund indicate any change in the program's objectives?

Dr. Duke: It would be more of an increased awareness of the need to deal with bioterrorist and chemical events. The PCC program was created in the time of a national public health crisis when poison control centers facing devastating financial crisis were forced to close. Of the more than 100 poison centers, almost one-third

closed in the last three years. Congress appropriated these funds to help in stabilizing the remaining centers and to ensure that this vital component of our public health infrastructure remains in place. PCCs are actively engaged in bioterrorism activities. For instance, PCCs were specifically identified in the HRSA Bioterrorism Hospital Preparedness grant guidance as a necessary member of the Statewide plan for bioterrorism. On the response front, during the anthrax terrorism in South Florida, the regional poison control center responded to more than 1400 telephone inquiries in 3 days from a variety of constituents including concerned parents and health care providers.

Mr. Regula: Can you describe how HHS bioterrorism research meshes with the extensive efforts in the Defense Department, such as the DARPA research of biological warfare post-exposure therapeutics and the defense-wide Chemical and Biological Defense Program?

Mr. Allen: NIAID and DoD have complementary roles in biodefense research, and a long history of productive collaboration in those roles. The role of NIH is to develop tools to protect civilians from potential agents of bioterrorism. The role of the DoD is to develop interventions to protect our troops against biological warfare. The threat of a bioterrorist attack against civilians differs in several important ways from biowarfare directed at military personnel. Civilian populations are more vulnerable to such attacks because of their diversity with regard to age and health status. Civilians, unlike military personnel, generally will not have received vaccines to prevent infections with microbes likely to be used as bioweapons. Moreover, the range of pathogenic microbes that might be used in a bioterrorist attack on civilians is much broader than what might be effectively used against the military. As we learned in the anthrax incidents of 2001, a bioterror attack against civilians is likely to be sudden and unexpected, requiring rapid diagnostics and therapies. Thus, the two agencies have somewhat divergent roles to play in the biodefense effort.

In that general framework, the NIH and DoD have a long-standing history of close and extremely productive collaboration, particularly with the US Army Medical Research and Materiel Command (USAMRMC), which directs most of the research for DoD's Joint Medical Chemical and Biological Defense Research Program, and USAMRMC's lead laboratories for biodefense and infectious diseases research, the US Army Medical Research for Infectious Diseases (USAMRIID) and the Walter Reed Army Institute of Research (WRAIR), respectively. NIAID is pleased with our relationship with USAMRMC, USAMRIID and WRAIR, which we believe represents a model for interagency collaboration in biomedical research. NIAID extramural staff have worked with USAMRIID and WRAIR staff for many years on a number of areas of joint interest, especially the development of vaccines for tropical and emerging diseases. That relationship has established a foundation upon which new collaborations to address issues of biodefense are being built, collaborations that leverage the strengths of each organization. For example, USAMRIID scientists have a wealth of experience built over many years of biodefense research aimed at developing vaccines against organisms

that are plausible candidates for use in a biowarfare attack, has many reagents that are of tremendous value to the broader scientific community in general, and has containment facilities that are required to carry out preclinical studies necessary to prove the value of vaccines or drugs against potential dangerous bacteria and viruses. NIAID has extensive preclinical drug and vaccine development resources, unparalleled clinical research experience and capabilities, reagent repository facilities, and virtually limitless access to the brightest minds in fundamental research, especially in the areas of microbiology and immunology. NIAID intramural scientists are also initiating scientific collaborations on several fronts, including studies on an Ebola vaccine candidate and the coordination of plans for construction of new biocontainment facilities on the grounds of Fort Detrick.

The DARPA program is another key component of the DoD involved in biodefense and biowarfare. DARPA is highly focused on high-risk projects to develop innovative interventions and diagnostics. NIAID is exploring the mechanisms used by DARPA as possible models for NIAID's product development effort. Many investigators involved in DARPA-funded R&D are also NIAID-funded for other related research. Finally, the DARPA program has major strengths in diagnostics, complementing NIAID's strengths in the areas of infectious disease research.

Mr. Regula: Are there mechanisms in place to ensure that HHS and DoD are coordinating their bioterrorism research work and targeting their efforts to their agency's relative strengths?

Mr. Allen: NIAID has a long-standing, close, and extremely productive collaborative relationship with a number of components of the DoD, including the Defense Advanced Research Projects Agency (DARPA) and biomedical research components within each of the Services. Most notable in the area of counter-bioterrorism research is NIAID's collaborative relationship with the U.S. Army Medical Research Institute for Infectious Diseases (USAMRID), located at Fort Detrick in Frederick, Maryland. NIAID is pleased with this relationship, which is built upon a base of complementary research efforts. NIAID staff have worked with USAMRIID staff for many years on a number of areas of joint interest, especially the development of vaccines for tropical and emerging diseases. That relationship has established a foundation upon which new collaborations to address issues of biodefense are being built that will leverage the strengths of each organization.

Mr. Regula: How does the Office of Emergency Preparedness (OEP) interact with the new US Freedom Corps supported out of the White House? I notice the proposed $10 million Medical Reserve Corps is described as being under USA Freedom Corps umbrella but funded out of the OEP budget.

Mr. Allen: There are many programs and initiatives supported under the USA Freedom Corps framework that are implemented or coordinated by federal agencies. For example, *Operation TIPS: Terrorist Information and Prevention System* is a project of the Department of Justice and the *Triple Community Emergency Response Team*

Members, also known as CERT, is a program conducted by the FEMA. The USA Freedom Corps, through the USA Freedom Corps Council and an Assistant to the President within the White House, makes policy recommendations to enhance service and works with key service agencies in government and the nonprofit sector to recruit and mobilize volunteers.

While the initial FY 2003 budget request of $10 million for development of a Medical Reserve Corps (as a part of the new US Freedom Corps) was requested in the budget of the Office of Emergency Preparedness (OEP), HHS intends that the program will be developed and maintained by the HHS Office of the Surgeon General (OSG). Because both OEP and OSG report to the Assistant Secretary for Health, there will continue to be a strong and ongoing collaborative effort between the two offices in the development and operation of the Medical Reserve Corps. In fact, OEP participated in the development of a "guide for Local Officials for the Establishment of a Citizen Volunteer MRC Unit". OEP also provided recommendations on which municipalities would likely be good sites for citizen volunteer MRC start ups, including advice on how the volunteer groups could be coordinated and/or integrated with existing Metropolitan Medical Response Systems (MMRS), which are funded and managed by OEP. Additionally, the OEP regional emergency coordinators, who provide local advice and assistance to states and localities, may also be used as local on-scene advisors during a community's development of citizen volunteer MRC units. It is anticipated that the citizen volunteer MRCs will be able to provide important surge capacity to address local mass casualty treatment needs.

OFFICE OF EMERGENCY PREPAREDNESS AND
OFFICE OF PUBLIC HEALTH PREPAREDNESS

Mr. Regula: How many FTEs are supported by the Office of Emergency Preparedness and the Office of Public Health Preparedness?

Mr. Allen: OEP's FY 2002 appropriation and the FY 03 President's Budget request supports 107 FTEs. The President's Budget initially projected using an average of 10 FTEs in 2002. As we seek to staff this office as rapidly as possible this number is subject to change.

Mr. Regula: How do the SERT teams (Secretary's Emergency Response Teams) differ from the ongoing efforts of the Office of Emergency Preparedness National Medical Response Teams and Disaster Medical Assistance Teams?

Mr. Allen: The primary resources for an HHS response are Disaster Medical Assistance Teams (DMATS) and Specialty Teams (NMRT, VMAT, DMORT) supplied by the National Disaster Medical System (NDMS), a federal, private partnership which dates back to 1982. Each time a NDMS team is deployed to provide health and medical support to a State and Local disaster relief, a Management Support Team (MST) is assigned to accompany the medical team. The MST provides management and control

of the HHS assets, as well as serving as a forward health and medical observation unit to conduct needs assessments and health and medical systems analysis, and to provide coordination of communications, transportation and management of a medical cache. This information drives the HHS asset allocations during the relief and recovery phases of the disaster.

HHS/OEP participates on a Domestic Emergency Support Team (DEST), led by the FBI, in support of the Special Agent-in-Charge (SAC) of an incident. The DEST provides technical assistance to the FBE Special Agent-in-Charge, and eventually becomes a part of the FBI Joint Operations Center. The DEST travels with its gear on DoD aircraft, and theoretically can be airborne within 4 hours of notification of an incident.

Current DOD aircraft restrictions limit the HHS DEST and Foreign Emergency Support Team (FEST) participants to two (2) for each team, and these are designated OEP employees who serve on the DEST and FEST call list as "ancillary duties".

The NDMS Management Support Team (MST) is comprised of personnel from different agencies within HHS and/or from a cross section of the private health and medical community and has been trained in all aspects of their position. The MST provides management and coordination for HHS health and medical specialty teams made up of medical personnel and support staff from all levels of government and the private sector.

There may be occasions, when the State and local officials require one or more of the health and medical teams to work with a local Incident Management Team. This situation might require a modified MST for coordination purposes that would be part of the local Incident Management Team. Depending on the need of State and local officials, the following assistance can be provided by the MST.

- Brief officials on the availability and capabilities of available and responding resources;
- Provide additional assessment capability;
- Provide a HHS health and medical official to be part of a Unified Command;
- Provide Technical Specialists to assist State and local teams;
- Prepare for the arrival, briefing, and assignment of DMATs and other response teams to disaster activities;
- Recommend appropriate health and medical measures to support disaster objectives;

- Recommend to officials the deployment of additional health and medical response resources as appropriate;

- Establish a system of re-supply for the MST and [field response teams] that does not diminish local resources;

- Manage teams to reduce workload on the local Incident Management Teams; and

- Manage teams to meet stated objectives and to provide for health and welfare of all health and medical response resources assigned.

The MST provides critical necessary functions in the response aspects of an event. They are not, however, designed to provide the top level liaison across the federal government and throughout the federal system. The critical core knowledge necessary to make judgement calls that will impact Departmental resource allocations for events such as bioterrorism will be provided by the SERT. The SERT team provides both the assets and professional talent for Departmental-level rapid assessment of an emergency involving a biological agent threat through the use of specifically designated senior health officials from the Department who have the requisete skills to liaise with pertinent Federal, State, and Local authorities, rapidly assess the public health and medical situation at the site, and who are able to communicate this information in a secure and ongoing fashion to the HHS leadership.

In November 2001, the Secretary created the Office of Public Health Preparedness (OPHP) to integrate the Department's emergency preparedness and response programs into a more efficient "One Department" Activity. OPHP is to direct the Department's efforts to prepare for, protect against, respond to, and recover from acts of bioterrorism and other public health emergencies and serve as the focal point within the Department for these activities. In the Functional Statement, OPHP is responsible for: Directing HHS OPDIVS and STAFFDIVS implementation of a comprehensive HHS strategy to protect the civilian population from acts of bioterrorism and other public health emergencies.

Under the authorities as set forth in the Secretary's Specific Priority Activities, OPHP recommends the establishment of four (4) specialize teams, which will be called the Secretary's Emergency Response Teams (SERTS) and will serve as the primary or lead HHS representatives to the DFO and as the Secretary's liaisons, will provide a "top management" level presence for the Department in the field.

METROPOLITAN MEDICAL RESPONSE SYSTEM

Mr. Regula: Your budget has a large increase for the Metropolitan Medical Response System, from $25 million to $50 million. Would this investment complete the effort to establish these systems in all major metropolitan areas?

Mr. Allen: The original intent of the MMRS program was to establish these systems in 120 of the largest metropolitan areas. The FY 2003 requested increase of $25 million will complete funding for the 25 MMRS begun in FY 2002, bringing the total number of MMRS to 122. The increase will also provide for auxiliary medical capacity activities in the MMRS areas.

Mr. Regula: The NIH bioterrorism budget includes $250 million to procure anthrax vaccine. Isn't procurement a function really within the jurisdiction of CDC, not NIH?

Mr. Allen: The nation has an urgent and compelling need to have a second-generation anthrax vaccine product quickly available. At the moment, a second-generation anthrax vaccine still needs to be developed and tested. Although it may be unusual for NIH to purchase a vaccine, in this case, there is logic to having NIH take the lead due to the accelerated nature needed to do the research, develop, test and purchase this vaccine in a short time. Ultimately, the vaccine, when purchased, will be managed by CDC as part of the national stockpile. No one is expecting that NIH will become a stockpile manager for this vaccine.

Mr. Regula: Is the purpose of the $10 million in your FY03 bioterrorism request different than the mental health treatment and post-traumatic stress funding SAMHSA received last year?

Mr. Curie: Yes, the purpose for the $10 million request in FY 2003 for bioterrorism is different than the funding received last year for mental health treatment and post-traumatic stress.

In FY 2002, $10 million from the Public Health and Social Services Emergency Fund was specifically intended to expand the National Child Traumatic Stress Initiative to support expertise in child trauma related to terrorism. This initiative established treatment development and community service centers to treat children who have experienced trauma, collected clinical data to further understanding of the developmental impact of trauma on children and the success of interventions, and developed a comprehensive resource center that provides education-oriented material for health professionals, children and the public.

The Terrorism/Bioterrorism preparedness and planning program proposed for FY 2003 will focus on assisting States in incorporating bioterrorism readiness and response into their emergency preparedness planning; behavioral health triage in health care settings, bioterror crisis intervention, and disseminating knowledge to public officials to prepare them in averting widespread public fear-induced over utilization of health care facilities and loss of confidence in public institutions.

Mr. Regula: I understand the program is still under development, but can you describe its general outlines? Will the funds go to State and local governments or be retained at the Federal level?

Mr. Curie: The proposed Terrorism/Bioterrorism preparedness and planning program will fund State and local organizations in developing solutions to the most concerning behavioral health aspects of bioterrorism, the large-scale consequences of fear-induced behaviors. This program will support:

- technical assistance to States to assist them in incorporating bioterrorism readiness and response into their State emergency preparedness planning;
- the development of methods to better discern the health needs of persons presenting to emergency facilities after a bioterror attack (behavioral health triage);
- the development of bioterror-specific crisis interventions techniques, and;
- the dissemination of knowledge to assist public officials in reducing widespread fear-induced behaviors including public fear and panic, overwhelming fear-induced utilization of hospital emergency rooms and other health care facilities, and loss of confidence in public institutions.

Initial stages of triage and crisis intervention activities will be devoted to defining and delineating the issues comprehensively enough to justify a credible on-the ground planning and response strategy; later stages will use that information to implement the strategy. Education and training activities will initially focus on development and refinement of materials, identifying and engaging the most relevant audience and providing education and training through the most efficacious means possible.

Mr. Regula: How well developed is the field of bioterrorism-related mental health? Does SAMHSA have in-house staff expertise in this area? What is the capability at the State and local level?

Mr. Curie: SAMHSA's long standing involvement in the response to the emotional consequences of disasters has repeatedly reinforced the importance of understanding and responding to the psychological effects of such events. While the field of bioterrorism-related mental health is in an early stage of development, a few models exist that help broaden our understanding of the issues.

Experience in Oklahoma City following one of the Nation's most significant terrorist crimes has shown us that man-made disasters result in more frequent, longer lasting, and more severe mental health consequences. Terrorist incidents have an impact on persons and communities far greater than the loss of life and property might suggest.

One could assume the terrorist use of biological weapons could impact the mental health of communities in a manner as great or even greater than that seen even in Oklahoma City.

SAMHSA has one expert in mental health related issues of trauma, including bioterrorism. In addition, there are several staff with expertise in emergency preparedness and crisis counseling. SAMHSA also provides grants to centers around the country to support best practices and serves to address post - traumatic stress disorder. Currently, State and local levels do not have the strongest capacity for responding to the mental health consequences of bioterrorism. One important aspect of the preparedness at the State and local levels is ensuring adequate behavioral health surge capacity. Surge capacity needs are highly dependent on accurate modeling scenarios (which do not currently exist) to determine the magnitude of behavioral casualties and efforts to develop appropriate bioterror crisis intervention techniques.

BIOTERRORISM PREPAREDNESS

Mr. Wicker: How vulnerable is our nation's water supply to a bioterrorist attack? How are the agencies involved in bioterrorism preparedness coordinating to prevent an attack on our water supply?

Mr. Allen: The United States public water supply system is one of the safest in the world. The general public should continue to drink and use water just as they would under normal conditions. Local water treatment suppliers and local governments are on the alert for any unusual activity and will notify the public immediately in the event of any public health threat. At this point, we have no reason to believe that additional measures need to be taken.

The U.S. Environmental Protection Agency (EPA) is the lead federal agency that makes recommendations about water utility issues. The EPA is working closely with the CDC and the U.S. Departments of Defense and Energy to help water agencies assess their systems, determine actions that need to be taken to guard against possible attack, and develop emergency response plans. For more information, visit <http://www.epa.gov/safewater>.

SMALLPOX

Mr. Wicker: How much protection from a smallpox outbreak exists for those who were vaccinated for smallpox before the use of the vaccination was terminated?

Mr. Allen: A high level of protection following a single vaccination against smallpox exists for about 3-5 years after the vaccination and good but waning protection can continue for up to 10 years following a single vaccination. People who were vaccinated more than once may have a longer period of protection, however, full immunity against disease also begins to decrease in these individuals as the time interval since vaccination increases. Individuals who were vaccinated in the early 1970's before routine vaccination was stopped may still have some residual immunity that could decrease their chances of dying from smallpox but they most likely do not have enough immunity to protect them from developing smallpox.

HHS EFFORTS TO PREPARE AGAINST BIOTERRORISM

Mrs. Northup: What is our greatest weakness in the area of Bioterrorism?

Mr. Allen: The greatest weakness is at state and local levels which, only now, are receiving the need resources to add needed staff and to plan for and develop programs to quickly detect and diagnose disease outbreaks; to be able to distribute drugs or vaccines to a large population over a 3-4 day period; to plan for a sudden surge of patients; and to be able to communicate expeditiously with hospitals, laboratories, infectious disease specialists; federal authorities; and law enforcement personnel. Personnel need to be trained; planning for large-scale distribution of products is complex; installing needed communications systems takes time. Progress is now being made and it is clear that the states have given this effort a high priority but it takes time to resurrect an infrastructure that has been allowed to deteriorate for so long.

Mrs. Northup: What is our greatest strength?

Mr. Allen: One of our greatest strengths is having a Department manned by devoted and skilled professionals. HHS has demonstrated it can accelerate efforts to enhance preparedness by moving State and local funding in record time while also providing guidance and putting a tracking process in place to ensure accountability. Secondly, the State and municipal work plans thus far reviewed have reflected an enormous State and local effort to enhance readiness and begin a planning process that is moving more quickly than anticipated. At Federal State and local levels, there is a level of commitment and willingness to work together, with increased effort to engage all stakeholders. This effort has resulted in excellent progress in a short period of time, and assurance that we do indeed have a public health system that Americans can count on, despite the fact that there has been historically a less than adequate investment in public health.

Mrs. Northup: What kind of threat do we think is most likely to occur? Do we think that it would be something like what happened with Anthrax, or do we think it would be most likely the use of agents against our armed forces fighting abroad?

Mr. Allen: Based upon recent intelligence reports, the most likely threat is that of an event involving a suicide bomber or an explosion of some sort causing mass casualties. We have learned that terror is now as much a local issue as it is for our troops fighting overseas.

The most likely biological threat is anthrax. We know that someone or some group was able to produce enough to cause serious problems, as happened last October. It is a certainty that there is more material out there somewhere. Smallpox represents a lesser risk, simply because it would be more difficult to obtain. However, if smallpox were to be released, it has the potential to result in a national and an international catastrophe if we are not able to control it.

Mrs. Northup: Since September 11, how have our efforts against bioterrorism changed focus?

Mr. Allen: Our efforts against bioterrorism have always been appropriately focused on enhancing Federal, state and local capacity to prepare and respond to a public health emergency, as well as on the research and development of safer and more effective treatments and vaccines against biological agents. Since September 11, the combination of both increased funding and the lessons learned from real-life scenarios have accelerated and focused our efforts on targeted priorities.

Mrs. Northup: Are most of the costs associated with preparing against bioterrorism one-time infrastructure costs to improve information systems, build pharmaceutical stockpiles, etc. or will these be ongoing costs?

Mr. Allen: Some of the costs are one-time infrastructure costs but a substantial proportion represents recurring costs. We need to think of our public health staff as we would think of National Guard or police -- a cadre of people whom we need to deal with infectious disease threats whether man-made or emerging suddenly out of Africa as did AIDS, or out of Asia, as have recent new influenza strains. There will be added costs for stockpiles as, for example, if we can develop a new vaccine against plague or Ebola virus, it would be important to have quantities of such vaccine available in case of an emergency.

As we develop and strengthen our bioterrorism preparedness programs, we are trying to identify sustainable strategies that work so as to avoid unnecessary costs and make the most out of available funds. However, the ability of our Nation to respond to future emergencies will be a reflection of continued investment in our public health system.

Mrs. Northup: Why are we focusing on improving our public health laboratories, when our best and most up-to-date research capabilities are part of our universities? Shouldn't we be capitalizing on their expertise and quality of labs to prepare against bioterrorism?

Mr. Allen: Public health laboratories are the diagnostic centers for detection of cases of threat diseases. University laboratories focus on research and development of assay and methods. A major emphasis next year will be to support academic research programs through NIH and connect them with the Laboratory Response Network.

Mrs. Northup: The NIH Budget request includes an increase of nearly $1.5 billion in 2003 for support of new research into bioterrorism agents and vaccines to fight them. The request includes funding for expanded research infrastructure to deal with the potential threats. What is the current capacity of the biomedical research community to address the impending threats?

Mr. Allen: There is enormous capacity in the research and development community to respond to the needs for research in all areas related to countering potential bioterrorism agents and emerging infections. However, this requires that we expand vitally important research infrastructure capabilities to do research on the biological agents most likely to be used for these purposes. The existing facilities in the U.S. are limited in number. Lack of access to these specialized resources is the most critical limiting factor to conduct research on these dangerous pathogens. The most urgent infrastructure needs are: (1) specialized, high containment facilities in which research of the most dangerous pathogens, including animal testing of vaccine and drug candidates, can be conducted safely and effectively; (2) specialized animal models, including non-human primates, that will mimic the pathogenesis of the diseases in the human body; and (3) repositories that make vital research materials, such as diagnostic and therapeutic reagents, available to scientists.

Mrs. Northup: If this funding intended to build adequate infrastructure, it is still in practicality, 18 months to two years away, what are we currently doing to insure an adequate response to protect the public from this threat?

Mr. Allen: The scientific community, throughout the academia, industry, and federal agencies, have rapidly responded with redirection of many research programs thereby increasing our research capability and capacity. While the actual building of the physical infrastructure and other critical, specialized resources will take time, much other work which is not dependent on these specialized resources have begun but must be expanded. Several examples include: completed dilutional studies on the existing smallpox vaccine which showed that through dilution of the product we can safely increase the number of effective doses by five-fold, to 75 million doses; developing second generation smallpox and anthrax vaccines; starting Phase I trials later this year on Ebola, West Nile Virus, and third generation smallpox vaccine candidates; and screening of current drugs for their therapeutic affect on these types of diseases.

Also, there are substantial amounts of basic research that can be and will be done while these specialized resources are being developed. For instance, researchers can and will use attenuated, related or non-virulent strains of the targeted pathogens to conduct their preliminary research. However, for many scientists, this type of research can only be carried so far before reaching a point where the work will stop unless the scientists have access to specialized, high-containment labs and specialized animal models to adequately test their concepts, theories and/or pre-clinical products, safely and effectively. Therefore, a key component of the NIAID strategic plan is to ensure that the critical, specialized resources become accessible to researchers in the next two to five years as the researchers start to need them.

Mrs. Northup: As I understand it, without the associated public health threat, the agents likely to be used by Bioterrorists would fall into the category of Orphan Diseases. With all the funding invested in the issue of Bioterroism, are there long-term benefits to the health of the general public that can be expected from this investment, above and beyond protection against the immediate threat?

Mr. Allen: In fact, many of the organisms in question, and a host of other emerging infectious diseases and drug-resistant microbes, already pose significant public health threats in many parts of the world. As we have seen many times, these same diseases can spread by natural routes and pose serious threats elsewhere. Thus, the positive long-term benefits for other diseases that will result from the large investment in both basic and translational research in biodefense will be substantial. Research on the microbial biology and pathogenesis of these organisms will enhance understanding of other more common and naturally occurring infectious diseases, both in the United States and around the world. Advancements in the arena of diagnostics, therapeutics, and vaccines will improve our ability to diagnose, treat, and prevent major killer-diseases, such as malaria, tuberculosis, HIV/AIDS, and a spectrum of emerging and reemerging diseases, benefitting people around the world. Basic research will greatly enhance our understanding of the molecular and cellular mechanisms of the innate immune system and its relationship to the adaptive immune system, and lead to improvements in the treatment and prevention of immune-mediated diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases. Finally, improved understanding of the mechanisms of regulation of the human immune system will have positive spinoffs for diseases such as cancer, immune-mediated neurologic diseases, and allergic and hypersensitivity diseases, as well as for the prevention of rejection of organ transplantation.

EMERGENCY SUPPLEMENTAL FUNDS

Mr. Obey: What progress has been made so far in obligating and utilizing the emergency supplemental funds provided to the Department of Health and Human Services in the FY 2002 Department of Defense Appropriations Act (PL 107-117)?

Mr. Allen: Of the $2.8 billion in supplemental funding, agencies have awarded $1.9 billion (67%) as of the end of April. Accomplishing this in the roughly three and a half months these funds have been available reflects the intense effort we are making to upgrade our defense against bioterrorism.

Mr. Obey: Do you expect to carry over any unobligated balances of these funds into FY 2003? If so, in what categories and why?

Mr. Allen: We do not currently anticipate carrying funds forward into FY 2003. The areas where carryover is most likely are one-time projects with significant lead time for contracts. For example, while NIH anticipates awarding the construction contract for the new BioSafety Level 4 facility at its Rocky Mountain Lab, it is possible that the design and subsequent construction contract work will not be completed until early in FY 2003. Similarly, there is some chance that some of the construction-related security funding, or command and control contracts may not be completely in place by the end of the fiscal year.

Mr. Obey: Please indicate the planned uses of the funds appropriated for the CDC in the Public Health and Social Services Emergency Fund in FY 2002, including both regular annual appropriations in PL 107-116 and emergency supplemental appropriations in PL 107-117. For each basic category of uses (such as improving internal CDC capacity), please indicate the anticipated expenditures for each major activity within that category.

Mr. Allen: The table follows:

Centers for Disease Control and Prevention
FY 2002 Bioterrorism & Emergency Activities Funding
(Dollars in Millions)

	FY 2002 Base Approp.	FY 2002 Supplemental	Total, FY 2002 BT Funding
Upgrading State & Local Capacity			
-- Consolidated State Grants	----	$865.0	$865.0
-- Health Alert Network	$34.0	----	$34.0
-- Laboratory Capacity -- Chemical	$7.5	----	$7.5
-- Technical Assistance & Oversight	$10.7	----	$10.7
-- Centers for Public Health Assistance	$20.0	----	$20.0
-- Partner Cooperative Agreements	$3.0	----	$3.0
Subtotal, State & Local Capacity -	**$75.2**	**$865.0**	**$940.2**
Upgrading CDC Capacity:			
-- Select Agents	$1.0	$3.2	$4.2
-- State/Local Technical Assistance & Oversight	----	$4.2	$4.2
-- Preparedness & Response	$7.9	$54.0	$61.9
-- Laboratory Capacity	$18.7	$18.5	$37.2
-- Surveillance & Epidemiology	$5.5	$8.5	$14.0
-- Research	$1.6	$11.7	$13.3
-- Anti-Infective Agents	$2.0	----	$2.0
Subtotal, CDC Capacity -	**$36.7**	**$100.1**	**$136.8**
National Pharmaceutical Stockpile	$52.0	$593.0	$645.0
Anthrax	$18.0	----	$18.0
Smallpox	----	$512.0	$512.0
Total, Bioterrorism -	**$181.9**	**$2,070.1**	**$2,252.0**
CDC Security Improvements	----	$46.0	$46.0
Critical Recovery Efforts	----	$19.5	$19.5
Total, Bioterrorism & Emergency Activities -	**$181.9**	**$2,135.6**	**$2,317.5**

Mr. Obey: What specific steps is the Department taking to ensure that city and county health departments receive an adequate share of the funds being provided under the CDC cooperative agreements with states for public health preparedness and response for bioterrorism?

Mr. Allen: State/local collaboration is an explicit requirement of the bioterrorism and public health preparedness funding. For grants to states, the guidance requires that funds benefit local efforts:

"All funding provided by CDC under this announcement is intended to benefit both state and local efforts for preparedness...Recipients should submit evidence that demonstrates meaningful collaboration, as outlined in the joint ASTHO-NACCHO Principles of Collaboration. It is expected that, in general, funding under the Cooperative Agreement will be allocated among the state and local public health agencies based upon the loci where Capacities are being developed."

States were asked to submit specific documentation of local public health agencies' involvement in work plan development, including letters acknowledging active involvement.

Inaddition to the 50 states, the District of Columbia, Chicago, New York and Los Angeles all received direct awards from CDC according to a population-based funding formula. These four jurisdictions account for 7.6% of the total funding available.

Mr. Obey: Based on the workplans received from the states, what information can you provide about the share of the FY 2002 supplemental funds for public health preparedness and response for bioterrorism that is likely to be utilized by local health departments?

Mr. Allen: States were not required to identify funding directed to local public health agencies. Therefore, CDC does not have complete data on the proportion of funds allocated directly to local areas. In follow-up with states, this specific data will be gathered. Although dollar figures are not available, ensuring collaboration and partnership with local public health agencies was a major focus of the technical review of the submitted work plans.

Mr. Obey: Section 319B of the Public Health Service Act, as added by the Public Health Threats and Emergencies Act of 2000, authorizes grants to states for assessment of their public health capacities and needs. Believing that a generally strong and capable public health system is an important element of defense against bioterrorism, Congress made grants under section 319B one of the permissible uses of the bioterrorism. preparedness funding provided in PL 107-117. Does the Department intend to use any of its FY 2002 funds for grants under section 319B of the Public Health Service Act?

Mr. Allen: The guidance for CDC bioterrorism funding for states (FY2002) does not require states to conduct a standardized assessment of broad-based public health capacities. However, as a first step to implementation of the full requirements of 319B, CDC's guidance requires assessments of public health system capacities related to bioterrorism, other infectious disease outbreaks, and other public health threats and emergencies to aid and improve planning, coordination, and implementation of state plans. The guidance does not explicitly require states to submit assessment results, but CDC plans to require such reporting as part of regular progress reports. CDC is working

on a plan to implement standardized, regular reporting of these aspects of 319B for the core capacities identified under 319A.

Mr. Obey: Does the Department intend to use any of the funds requested in its FY 2003 budget for this purpose?

Mr. Allen: CDC will continue preliminary implementation of these provisions with the funding requested for Bioterrorism.

Mr. Obey: If not, does the Department have any plans to implement the section 319B assessment process in the future?

Mr. Allen: CDC has collaborated with state and local officials to develop a rapid assessment tool and a broader performance assessment model for the evaluations authorized under 319B. However, CDC has not required a standard assessment tool or process in the recent Funding Guidance, preferring to allow state flexibility in the current year of the cooperative agreement program. States may choose to use these tools to perform assessments required under the cooperative agreement program.

Mr. Obey: To what extent do you believe that any of the activities now being funded under the bioterrorism. and public health cooperative agreements are an adequate substitute for the section 319B assessment process?

Mr. Allen: States are not required to use a standard assessment process that would fully implement the evaluation program described in 319B; however, CDC has made standard assessment tools available for states to use, voluntarily. CDC has not required a standard assessment tool or process, preferring to allow state flexibility in this phase of the cooperative agreement program.

Mr. Obey: What steps is the Department taking in FY 2002 to improve preparedness to deal with possible chemical terrorist incidents and threats, including assistance to state and local health departments and laboratories? What steps does the Department plan to take in FY 2003?

Mr. Allen: In June 2002, HHS contracts totaling $9.2 million will help 23 more U.S. cities prepare for rapid, coordinated medical response to large-scale public emergencies. The contracts are for development of additional Metropolitan Medical Response Systems (MMRS). The contracts will enable cities to coordinate emergency first responders, public health systems and hospitals to better respond to the needs of their citizens in times of crisis. With 97 cities already aided by HHS under the MMRS program, June's awards bring the total number of cities in the system to 122. The funds will help cities throughout the country deal with the public health consequences of disasters of all kinds. MMRS pulls together local fire and emergency medical services, hospitals and public health officials, and law enforcement responders in a united and well-coordinated effort to protect the public.

CDC's FY 2002 Supplemental Funds for Public Health Preparedness and Response for Bioterrorism awarded over $900 million to states to further strengthen the infrastructure to respond to public health threats, including chemical terrorist incidents. Preparedness planning, surveillance, communications systems, public information, and training programs will serve to prepare the public health system generally to deal with either chemical or biological attacks. For example, the guidance in the supplemental award includes a required activity for states to "develop operational plans and train personnel to collect, process, and transport blood and urine samples to CDC, or a CDC supported laboratory, for analysis of chemical agents. Plans should be consistent with CDC supplied protocols." These are the basic laboratory capacities needed in a possible chemical event.

In the FY 2002 supplemental award, five states were funded ($7.5 million) specifically to develop chemical laboratory capacity. Long-term, these state laboratories will form the basis of regional chemical laboratory response systems. So far, these laboratories have received analytical methods for the major nerve agents (including sarin gas that was used in Japan in 1995, soman, tabun and VX) and the sulfur mustard agents (generally known as the blistering agents). They are in the process of receiving methods for cyanide based compounds and lewisites. Outside of CDC and these five state labs, there are no labs that currently have available measurements of a broad panel of chemical agents as is done in the Rapid Toxic Screen. CDC is discussing transfer of the Rapid Toxic Screen methods with other Federal laboratories, including DOD and the FBI.

Cost estimates for FY 2003 laboratory capacity are currently under review, however, CDC expects FY 2003 funding levels to be comparable to those of FY 2002. In FY 2003, CDC plans to continue to do research (including animal studies and development of methods to measure chemical agents in blood and urine) on priority chemical agents that should be in the Rapid Toxic Screen. CDC will be emphasizing research on decontamination of blood and urine samples (killing infectious agents) using techniques that do not interfere with the measurements of chemical agents. Decontamination of blood and urine samples is important for safe handling of clinical specimens in the chemical laboratory. Special attention will be given to techniques other than gamma irradiation. CDC will also be working to simplify analytical methods so more methods can be transferred to state laboratories. Methods for approximately six more chemical agents will be transferred to five state laboratories. CDC will continue to meet with federal partners to be sure the capabilities of multiple federal laboratories is properly utilized in response to a chemical terrorism event. In FY2003, CDC will be establishing a Level 1, Level 2, and Level 3 response for its chemical laboratory to handle blood and urine samples in the ranges of 1-50 per day, 51-200 per day and more than 200 per day respectively. This multi-level design will improve the efficiency of the laboratory response by better targeting of resources and training of response laboratorians.

Mr. Obey: I understand that the Department may view its laboratory preparedness role with respect to chemical incidents as largely limited to preparing to analyze human clinical samples (as distinct from suspicious substances themselves and other samples drawn from the environment). If so, which federal agencies have responsibilities for analysis of environmental samples and what is the basis for this division of responsibilities?

Mr. Allen: For chemical agents likely to be used by terrorists, CDC focuses on analysis of human samples usually using blood and urine (for more detail see answer to R. 13). Environmental samples, including air, soil/dust, and water samples, are analyzed by EPA. The EPA role in environmental monitoring is specified in the Federal Response Plan. CDC and EPA have worked on coordinating these laboratory responsibilities so the two organization can share laboratory results during a chemical terrorism event.

ENHANCED METROPOLITAN RESPONSE SYSTEMS

Mr. Obey: In the event of a chemical terrorist incident (or threat or fear of such an incident) isn't it likely that state and local public health laboratories will be called upon to handle and analyze environmental as well as human samples? What federal assistance is available to help state and local public health laboratories prepare for such a task?

Mr. Allen: State and local laboratories may well be called on to analyze environmental as well as human samples. These laboratories should contact their regional EPA office for assistance, if it is needed. EPA has internal capability and some contracts to use specialized laboratories to measure chemical agents in environmental samples.

This year, (FY 2002) CDC is providing $7.5 million in funding to state laboratories in New York, Virginia, California, Michigan and New Mexico to improve their laboratory capability to measure chemical agents in human blood and urine. Long-term, these state laboratories will form the basis of regional chemical laboratory response systems. The analytical instrumentation purchased for this would be the same kind of instrumentation needed to analyze environmental specimens and persons that are being hired for chemistry expertise could also work on environmental samples.

On June 12 and 13, 2002, CDC will be hosting a meeting with laboratory representatives from EPA, FBI, CIA, DOD, USDA, FDA, DOE and selected states to help coordinate the federal laboratory response to chemical terrorism so states have a clearer understanding of how they can interact with federal laboratories. Included in this meeting will be discussion on coordinating measurements in environmental samples and measurements in blood and urine.

June's contracts total $9.2 million, or $400,000 for each city. The enhanced metropolitan response systems typically cost about $2.5 million, and are primarily paid for by local government.

The 25 cities receiving first-year contracts today include (by state):

Alabama -- Huntsville
Arizona -- Glendale
California -- Fremont; Bakersfield; San Bernardino; Modesto/Stanislaus County
Connecticut -- Hartford
Florida -- Fort Lauderdale; Orlando
Indiana -- Fort Wayne
Kansas -- Kansas City/Wyandotte County
Louisiana -- Marrero/Jefferson Parish
Massachusetts -- Springfield; Worcester
New York -- Syracuse
Ohio -- Warren
Rhode Island -- Providence
South Carolina -- Columbia
Tennessee -- Chattanooga; Knoxville
Texas -- Amarillo; Irving
Virginia -- Arlington

Cities receiving MMRS contracts are selected based on their population size. This is the fifth group of cities to be awarded MMRS contracts since 1996.

The MMRS concept was initially developed with HHS leadership in the Washington, D.C., area to coordinate emergency response among District of Columbia, Maryland and Virginia emergency and medical response jurisdictions. The concept was then applied in Atlanta, Ga., to help the city prepare for the 1996 Olympic Games.

MMRS planning specifically addresses early identification of the specific hazards, protection of the public from dangerous exposures, mass patient care and fatality management, and environmental safety.

In addition to Washington, D.C., and Atlanta, other cities which have received MMRS contracts since 1996 are:

Alabama – Birmingham; Mobile; Montgomery
Alaska -- Anchorage
Arkansas -- Little Rock
Arizona -- Phoenix; Tucson; Mesa
California -- Los Angeles; San Francisco; San Diego; San Jose; Long Beach; Oakland; Sacramento; Fresno; Santa Ana; Anaheim; Riverside; Glendale; Huntington Beach; Stockton
Colorado -- Denver; Aurora; Colorado Springs
Florida -- Miami; Jacksonville; Tampa; St. Petersburg; Hialeah
Georgia -- Columbus
Hawaii -- Honolulu

Illinois -- Chicago
Indiana -- Indianapolis
Iowa -- Des Moines
Kansas -- Wichita
Kentucky -- Louisville; Lexington/Fayette
Louisiana -- New Orleans; Baton Rouge; Shreveport
Maryland -- Baltimore
Massachusetts -- Boston
Michigan -- Detroit; Grand Rapids
Minnesota -- Minneapolis; St. Paul
Mississippi -- Jackson
Missouri -- Kansas City; St.Louis
Nebraska -- Omaha; Lincoln
Nevada -- Las Vegas
New Mexico -- Albuquerque
New Jersey -- Newark; Jersey City
New York -- New York City; Buffalo; Rochester; Yonkers
North Carolina -- Charlotte; Raleigh; Greensboro
Ohio -- Columbus; Cleveland; Cincinnati; Toledo; Akron; Dayton
Oklahoma -- Oklahoma City; Tulsa
Oregon -- Portland
Pennsylvania -- Philadelphia; Allegheny County
Tennessee -- Memphis; Nashville
Texas -- Houston; Dallas; San Antonio; El Paso; Austin; Fort Worth; Arlington; Corpus Christ; Garland; Lubbock
Utah -- Salt Lake City
Virginia -- Virginia Beach; Norfolk; Richmond
Washington -- Seattle; Spokane; Tacoma
Wisconsin -- Milwaukee; Madison

Altogether HHS has provided more than $62.2 million to support MMRS systems since 1996.

The HHS-led emergency response system includes the National Disaster Medical System (NDMS), a partnership of federal agencies and the private sector. The NDMS also comprises more than 8,000 private sector medical and support personnel organized into 80 disaster assistance teams. These teams are deployed to provide immediate medical attention to the sick and injured during disasters, as well as mortuary and veterinary care, when local emergency response systems become overwhelmed. The HHS Office of Emergency Preparedness oversees the NDMS.

LABORATORY RESPONSE NETWORK AND NATIONAL ELECTRONIC DISEASES SURVEILLANCE SYSTEM

Mr. Obey: What are your current goals for development of the Laboratory Response Network (LRN) , in terms of measures such as the number of labs participating at each level and the capabilities of those labs? Where does the network stand now relative to those goals? Where do you expect the network to stand relative to those goals at the end of FY 2003? At what point do you expect your current goals for the Laboratory Response Network (LRN) to be met?

Mr. Allen: The information follows:

Laboratory Response Network for Bioterrorism

The Laboratory Response Network for Bioterrorism (LRN) is an integrated network of public health and clinical laboratories that provides laboratory diagnostics and disseminated testing capacity to support public health preparedness and response to an act of bioterrorism. A primary goal of the LRN is to ensure that all member laboratories collectively maintain state-of-the-art biodetection and diagnostic capabilities as well as surge capacity for all biological and chemical agents likely to be used by terrorists. The LRN is based on use of standard protocols and reagents, integrated data management, and secure communications. Eligibility for membership at levels B and C is currently limited to State and local public health and selected Federal level laboratories. At optimal membership level, the LRN is expected to maintain approximately 250 registered facilities (Level B and Level C labs). As the threat agents change and as technology improves, the labs will maintain and enhance their capacity accordingly.

Established in FY 1999, the LRN is currently funded with Bioterrorism Public Health and Social Services Emergency Funds under Upgrading CDC Laboratory - Biological Agents.

In order to implement the strategic vision of the LRN, the operational plan has been divided into five critical programmatic components: 1) LRN secure website and electronic communications, 2) LRN technology transfer for threat agent detection capability, including proficiency testing, 3) LRN infrastructure building for response capacity, 4) LRN integration for preparedness and response interoperability, and 5) LRN planning and evaluation. This operational system is being expanded, through collaboration with key partners, to provide biological threat agent testing capability and surge capacity for the clinical, environmental, food-borne and waterborne sample matrices. In parallel, the LRN is working with the National Electronic Diseases Surveillance System (NEDSS) initiative to ensure the solutions developed for electronic reporting of BT lab test results and lab capacity monitoring will be NEDSS compatible.

LRN Current Capacity

The LRN is a four-tiered system designed to link state and local public health laboratories with advanced capacity clinical, military, veterinary, agricultural, food, and water testing laboratories. The LRN collaborative partnership operates as a network of laboratories with progressively stringent levels of safety, containment and technical proficiency necessary to perform the essential rule-out, rule-in and referral functions required for agent identification. Network access provides all member laboratories with the means to accept and transfer specimens to appropriate facilities where definitive testing can be undertaken.

- Level A - Clinical and academic laboratories (Level A) comprise the initial tier. These labs, which are self identified and may number as high as 25,000 facilities, are not provided password-protected website access for reasons of laboratory safety and network security. They are able to rule out specific agents and forward suspect samples to a higher level laboratory.

- Level B - Level B labs are able to rule out specific agents; forward specimens to a higher level lab; process ennviromental samples; and perform confirmatory testing and susceptibility testing. These laboratories are state and county public health labs using Biosafety level - 2 (BSL-2) with BSL-3 practices. As of June 3, 2002, 54 state and local public health laboratories are Level B members.

- Level C - Level C laboratories labs are able to perform all activities that Level B labs do and have the advanced capacity to perform nucleic acid amplication assays, molecular typing, toxicity testing and provide surge capacity. These laboratories are state and local public health labs using BSL-3 facilities and practices. As of June 3, 2002, 49 state and local public health laboratories are Level C members.

- Level D - These laboratories are able to perform all functions of Levels A-C. In addition, these laboratories can validate new assays; detect genetic recombinants; provide specialized reagents; bank isolates; and perform molecular typing for the smallpox virus. Only CDC and USAMRIID are classified as Level D.

All 50 states now have the capability to perform presumptive and confirmatory laboratory identification methods for Bacillus anthracis (anthrax), Yersinia pestis (plague) and Francisella tularensis (tularemia), as well as access to specialized laboratories for confirmation of Brucella species (brucellosis), and Clostridium botulinum toxin (botulism). In July 2002, the LRN will post on the restricted website provisional protocols for laboratory identification of alphaviruses (EEE, WEE, VEE viral encephalitides), Coxiella burnetii (Q fever), Burkholderia mallei (glanders), ricin toxin, and staphylococcal enterotoxin B, as well as the referral procedures for suspect specimens involving filoviruses (Ebola and Marburg hemorrhagic fevers) and arenaviruses (Lassa fever and Junin hemorrhagic fever). Discussions are in progress to

update guidance on the testing algorithm for varicella, vaccinia and variola. LRN members maintain competence in chain of custody procedures so that material evidence collected can be used in criminal proceedings.

The LRN leadership is a partnership between CDC and APHL, with oversight provided by a committee of LRN partners from CDC, APHL, Federal Bureau of Investigation (FBI), Department of Defense (DoD), and American Society for Microbiology (ASM). The strength of the network is also derived from collaborations with the DoD (Army, Navy, Air Force), DOJ (FBI), DOE (Lawrence Livermore National Laboratory), FDA (Center for Food Safety and Nutrition and Center for Devices and Radiological Health), USDA (National Veterinary Service Laboratory and Food Safety Inspection Service), EPA (Office of Research and Development) and NIH (Office of Research Services), as well as public health organizations and professional societies (APHL, ASM), thus leveraging not only highly developed expertise but also galvanizing larger networks for emergency response and overall continuity of operations. Additionally, the LRN has established international partnerships with Canada and the United Kingdom and is in the process of formalizing a relationship with Australia

Selected highlights of LRN Basic Operational Time line for FY 2002-2004

Projected FY 02 Outcomes:

- update and revise lab protocols for current biological threat agents on restricted LRN website
- address lab protocol requirements for environmental sampling and testing
- launch new LRN B/C level lab protocols and reagents for remaining critical agents
- update and add LRN Level A lab protocols for current bio-threat agents on public access
- incorporate new rapid screening assays (PCR and TRF real time assays) into testing algorithm
- evaluate select commercial hand-held assays often used by Hazmat first responders
- integrate current testing algorithms with epidemiological case definitions and response plans
- prepare draft lab protocols for food-borne testing
- obtain FDA approval (510k) for in vitro diagnostic use of select B. anthracis and Y. pestis tests
- launch near-term electronic communication application for specimen tracking and test reporting
- expand LRN domestic partnership by 50 lab facilities
- provide anthrax vaccination to LRN laboratory personnel
- provide training to LRN B/C level lab trainers on rapid real time methods
- provide training to LRN A Level labs

- provide proficiency testing program to LRN B/C level member labs
- upgrade restricted website security and provide lab-user enhancements

Projected FY 03 Outcomes:

- update and revise lab protocols for all biological threat agents on LRN website
- launch lab protocols and reagents for food-borne testing matrix
- prepare draft lab protocols for waterborne testing
- obtain FDA approval (510k) for in vitro diagnostic use of select bio-threat agent tests
- launch mid-term electronic communication application for client-side parsing of test results
- expand LRN domestic partnership by 50 labs to increase environmental and food-borne capacity
- expand LRN international partnerships to include official relationship with WHO
- provide funding and site visits to States, especially in regard to BSL-3 renovations and biosecurity
- provide ongoing training to LRN B/C level labs for specialized methods in protocols
- provide training and proficiency testing to LRN A Level labs (clinical)
- upgrade restricted website relative to user authentication security and use of LOINC codes
- upgrade restricted website to provided mirrored backup(s) for increase site stability and availability
- hold LRN partnership strategic planning meeting to update gap analysis and threat agent list

Projected FY 04 Outcomes:

- update and revise all lab protocols for biological and chemical agents on LRN website
- launch lab protocols and reagents for waterborne testing matrix
- incorporate new rapid screening assays (PCR and TRF) into testing algorithms
- develop new multiplex screening assays for biothreat agent panel
- obtain FDA approval for in vitro diagnostic use of new rapid screening assays
- launch NEDSS electronic communication application which uses HL7 messaging
- expand LRN domestic partnership by 25 labs to increase capacity for waterborne testing
- expand LRN domestic partnership by 10 labs to provide disseminated chemical testing
- provide funding and site visits to States and monitor readiness of enhanced infrastructure
- continue training and proficiency testing to LRN Level A, B, and C labs

- upgrade restricted website for interoperability and data exchange with key clinical entities

NATIONAL LABORATORY SYSTEM DEMONSTRATION PROJECT

Mr. Obey: What is the current status of the National Laboratory System demonstration project? How many states (or other geographic areas) currently participate in this program? Would this number increase under your FY 2003 budget? Have other states or areas expressed interest in participating? What would be the cost of adding additional sites to the National Laboratory System?

Mr. Allen: CDC currently supports four demonstration projects in Nebraska, Minnesota, Michigan, and Washington. The goal of the National Laboratory System (NLS) is the assurance of available, consistent laboratory testing capacity for public health practice across the nation by connecting private laboratories to the public health system. The NLS vision is a strong system of integrated public health, hospital, and independent laboratories at the local, state, and national level -- working in concert to protect the health of the Nation's citizens. The core strategy to build the NLS is the integration of the work of the 170,000 clinical laboratories with public health. This is critical for the day-to-day practice of public health, and essential for emergency operations to ensure secure/rapid transport of specimens, rapid/accurate diagnosis, linking lab results with epidemiologic investigations, chain of custody procedures, and etc. NLS will assure preparedness for bioterrorism (BT) and other public health threats through assessment, policy development, planning, and assurance of quality public health testing practice in clinical laboratories.

Core strategic elements of the NLS include:

- Assessment and monitoring of public health testing practices in clinical laboratories.
- Development of policies and plans to improve public health testing in clinical laboratories.
- Improvement of testing through training, disseminations of best practices and guidelines, and other system enhancements.

The National Laboratory System (NLS) includes not only the current 82 laboratories in the Laboratory Response Network (LRN), but also includes the hospital and independent laboratories throughout the country. In order for public health to know of the presence of various infectious agents (including those that may be used as agents of bioterrorism), there must be a close link with private sector laboratories. Therefore, the National Laboratory System is inclusive of all public health and clinical laboratories.

The Laboratory Response Network (LRN) is a group of laboratories (primarily state public health and federal laboratories) that have the capability of confirming the identification of certain select agents such as Bacillus anthracis, Francisella tularensis,

etc. As members of the Network, they have access to protocols and reagents on a secure website. All state public health laboratories are members of the LRN. Emergency response capcbilities extend the LRN to approximately 230 laboratories.)

The need to develop these linkages is recognized and included in Focus Area C in the Guidance for Fiscal Year 2002 Supplemental Funds for Public Health Preparedness and Response for Bioterrorism. Therefore, states that have interest in participating can choose to use these funds to establish the linkages and conduct the activities that are part of the NLS strategy. The cost for each state would be approximately $170,000 - $300,000.

The ultimate goal of the pilot efforts is to develop the model for a truly seamless, integrated, and complementary national system of laboratories. While each category of laboratories has-and will continue to have--its own unique responsibilities, the National Laboratory System will ensure that testing practices, shared responsibilities, and working relationships are adequately addressed, strengthened, and operating at the highest levels. In addition to needs identified for bioterrorism, there are numerous additional public health areas in which inconsistencies now exist. Examples include:

- Practices associated with isolation and identification of E. coli O157:H7 (a significant causative agent of hemorrhagic colitis) that led to under-reporting of disease.
- Practices associated with determination of antimicrobic resistance that led to both falsely identified resistant strains of bacteria and lack of recognition of resistant strains.
- Practices associated with laboratory diagnosis of Lyme disease that led to over-reporting.

HEALTH ALERT NETWORK

Mr. Obey: What is the current status of the Health Alert Network? I believe one of the benchmarks the Department has set for development of that network is to have local health departments serving 90 percent of the population connected to the network. Have I correctly described the goal? At what point do you expect that goal to be reached? Would additional funding accelerate the process?

Mr. Allen: Currently, 68% of all counties have continuous, high-speed Internet connectivity. Most local health agencies (67%) have a system for sending urgent health alerts to targeted community groups. Under the supplemental grant guidance, states must establish a method for 24/7 flow of information to local health officials, hospital emergency rooms, and law enforcement officials. Seventy percent (70%) of local health jurisdictions currently have the capacity for round-the-clock operability.

Connectivity is an integral component of the FY 2002 Supplemental Funds for Public Health Preparedness and Response for Bioterrorism, which is the large state bioterrorism grant awarded early this year. Critical benchmarks 11 and 12 specifically address required elements for connectivity. States are expected to have 90% of their population covered by the Health Alert Network by August 2003. In order to meet this critical benchmark, the state health department should have connectivity to all local health departments/jurisdictions in addition to hospitals and other emergency response agencies. The ultimate goal is 100% of the U.S. population be served by a local public health jurisdiction connected to the Health Alert Network.

Availability of information infrastructure developed in phase I of the Health Alert Network initiative now allows for use of the infrastructure to inform and train local public health practitioners across the nation.

Mr. Obey: Do you have goals or benchmarks for extending the Health Alert Network beyond health departments, to reach hospitals, clinics, health care providers, emergency response personnel, and others? In roughly how many areas does the network currently reach all or any of these potential participants? What is your current timetable for meeting any goals for expansion you have set?

Mr. Allen: The FY 2002 supplemental grant guidance requires states to "ensure effective communications connectivity among public health departments, healthcare organizations, law enforcement organizations, public officials, and others" by August 2003. Because funding for expanded connectivity has just been received, firm data is not yet available on the level of connectivity for these additional partners. CDC is now collecting this data and will provide it to the committee by June 30, 2002. Also, the Health Alert Network initiative funds advanced practice sites in Denver, CO; Atlanta, GA; and Rochester, NY to develop models for extending the network beyond health departments to reach hospitals, clinics, healthcare providers, and emergency response personnel; a detailed report developed by the National Association of County and City Health Officials (NACCHO) is available on that work.

NATIONAL ELECTRONIC DISEASE SURVEILLANCE SYSTEM

Mr. Obey: What is the current status of the National Electronic Disease Surveillance System (NEDSS)? Is NEDSS currently in use in any areas or programs? What progress would be made on development and implementation of NEDSS under your FY 2003 budget?

Mr. Allen: Prior to the issuance of the FY 2002 supplemental cooperative agreement award, 50 states, 6 cities, and 1 territory have been funded for NEDSS; 43 started with an assessment and planning phase. Sixteen states have received funds to develop their own systems that meet the NEDSS standards. At the National NEDSS Stakeholders meeting May 8-10, 2002, seven of these states demonstrated systems in use in their states which deliver at least some of the NEDSS functionality.

Nineteen states and one city have received funding for deployment of the NEDSS Base System, a NEDSS compatible system for state and local use under development by the Computer Sciences Corporation. Two of the states are currently field testing the pilot version of the NEDSS Base System. The other jurisdictions are assessing security and information technology infra-structure needed for successful deployment of version 1.0 of the NEDSS Base System later this summer.

Enhancement of NEDSS capacities were an integral component of the FY 2002 supplemental guidance and state award to improve bioterrorism preparedness and response. State NEDSS Coordinators were encouraged to work closely with their Bioterrorism coordinators and colleagues in preparing responses to this announcement for use of these new resources within their jurisdictions. Specifically "CDC encourages applicants to coordinate activities with relevant efforts currently underway in their jurisdictions or proposed under the various Focus Areas of this cooperative agreement program." "For those states that currently receive funds from CDC, the proposed activities should augment, complement, or be closely coordinated with those supported by other CDC programs (e.g. Emerging Infections Program (EIP), infectious disease Epidemiology and Laboratory Capacity (ELC) Program, National Electronic Disease Surveillance System (NEDSS)....." In addition, this program announcement allowed funds to be used for development or enhancement of NEDSS capabilities. Expectations of how the states plan to use these funds for NEDSS will be compiled from the workplans the states submitted in April. In FY 2003, CDC plans to continue the deployment of the NEDSS Base System as requested by states, incorporate needed enhancements in the NBS, and work with partners such as environmental health tracking to accelerate progress to a fully standards based, integrated public health information infra-structure.

CDC'S BUILDINGS AND FACILITIES

Mr. Obey: What is the current status of the major CDC buildings and facilities projects relevant to bioterrorism and public health preparedness, including the Emerging Infectious Disease Lab, the Scientific Communications Center, the Environmental Toxicology Lab, and any other projects you consider relevant? In each case, please indicate the purpose of the facility, the stage of planning or construction, when construction is expected to begin (where it hasn't begun already), when the facility is expected to be ready for occupancy, and what additional funding (beyond amounts already appropriated) will be needed to complete and occupy the facility.

Mr. Allen: The Emerging Infectious Diseases Laboratory (EIDL) will contain core (biological) BT and Rapid Response labs as well as provide urgently needed modern lab space for ongoing infectious disease research. The EIDL is anticipated to reduce the number of laboratorians working in substandard conditions at the Roybal Campus. The project also contains a Central Utility Plant (CUP) required to serve the EIDL and to provide backup capacity to the existing older CUP. The EIDL and CUP are both under construction and are expected to be operational by mid-2004.

Both projects are fully funded for construction, with $12 million requested in FY2003 B&F for the purchase of movable scientific equipment.

The Scientific Communications Center (SCC) will greatly enhance CDC's ability to communicate public health information of all types, including BT-related information, to all state, local and territorial health offices in "real time." CDC's Public Health Network broadcast and webcast studios and other support functions will be located in the SCC. CDC plans to award the construction contract for the facility in mid-July 2002, with construction start in late Summer 2002. Plans for occupancy of the facility are mid-2005. In addition, CDC has requested $21 million in FY 2003 B&F to complete the purchase of the specialized communications and AV equipment required to make the SCC operational.

The Environmental Toxicology Lab (ETL) will contain core (environmental and chemical) BT and Rapid Response labs as well as provide urgently needed modern lab space for ongoing environmental health research. The ETL will eliminate the number of environmental health laboratorians working in substandard conditions at the Chamblee Campus. The project also contains a Central Utility Plant required to serve the ETL and the entire Chamblee Campus. CDC plans to award the construction contracts for the ETL and CUP in September 2002, with construction commencing in the fall of 2002. Both facilities would be operational in late 2004.

CDC has requested $12 million in FY2003 B&F to complete the construction funding for the ETL and CUP.

Ft. Collins Replacement Lab Project

The architectural programming for Ft. Collins will be underway by the end of May 2002. The programming effort will determine the size and composition of the new facility. The new facility will be larger than the existing facility. CDC plans to produce a detailed project budget and implementation schedule by September 2002, that will provide the milestone design and construction dates for the project. CDC will make every effort to have the new facility ready for occupancy by 2007 – the expiration date of the existing lease.

East Campus Consolidated Lab Project, Phase I Infrastructure (Phase I), and Transhipment Center (Building 20)

This project includes significant upgrades, expansion, security enhancements, and modernization of the existing electrical and other major campus-wide utility systems at the Roybal Campus. Funding to date includes $25 million for Phase I Infrastructure from FY2002 B&F, and $32 million from FY2002 Security Appropriation for the Transshipment Facility. Because of the overlapping physical location of the projects, and the required engineering connections, Phase I Infrastructure and Transshipment will be designed and constructed as a single project.

BIOTERRORISM

Mr. Obey: Please describe CDC's activities aimed at preventing misuse of pathogenS with potential for terrorist use (including, but not necessarily limited to, enforcement of the "select agent rule").

Mr. Allen: The Antiterrorism and Effective Death Penalty Act of 1996 (Pub. L. 104-132) authorizes the Secretary of Health and Human Services (HHS) to regulate the transfer of certain biological agents (select agents) that have the potential to pose a severe threat to public health, and are of potential use by terrorists. The Centers for Disease Control and Prevention (CDC) is the agency within the Department responsible for promulgating this regulation under 42 CFR 72.6, additional Requirements for Facilities Transferring or Receiving Select Agents. This regulation went into effect on April 15, 1997 and is designed to ensure that select agents are not shipped to parties within the United States who are not equipped to handle them appropriately, or who otherwise lack proper authorization for their requests. Under this regulation, facilities wishing to transfer select agents are required to register with CDC. CDC is required to 1) maintain data on registered facilities; 2) CDC may inspect those facilities to ensure that they are capable of safely working with and transferring select agents; 3) CDC must maintain data on shipments of select agents between registered facilities; and 4) work with law enforcement agencies when violations of the regulation occur or are suspected of having occurred. This database is used for tracking interstate shipments of certain etiologic agents that could be used for bioterrorism purposes.

The Public Health Service Foreign Quarantine regulations (42 CFR 71.54) govern the importation, or subsequent distribution by transfer within the United States, of any etiologic agents, hosts, or vectors of human disease. A permit issued by the Office of Health and Safety(OHS) at CDC, Etiologic Agent Import Permit Program is required for such importations or distributions. The system tracks and issues permits for the international importation of etiologic agents that could be used for bioterrorism purposes.

SELECT AGENTS

Mr. Obey: How many full-time-equivalent employees were engaged in these activities in FY 2001? How many do you project to have engaged in these activities in FY 2002 and FY 2003?

Mr. Allen: In FY2001 there were nine FTEs working with the Select Agent program. Final apportionment of FTEs to the Select Agent Program in FY 2002 and FY 2003 is currently under review as a result of newly enacted legislation. Currently, 12 new FTEs have been approved for FY2002 (21 total FTEs), and CDC is actively working to hire those positions before the end of the fiscal year.

Mr. Obey: How many laboratories and other entities were registered under the select agent rule at the end of FY 2001? How many do you expect to have registered at the end of FY 2002?

Mr. Allen: CDC registered 55 facilities in FY2001. On average, CDC receives 55 new application a year, however, CDC has received over 75 new applications for registration this fiscal year. CDC has registered 347 facilities to date. With the new legislation, the number that will now need to register may increase to the thousands.

Mr. Obey: How many inspections of facilities registered under the select agent rule were conducted in FY 2001? How many inspections do you expect to conduct in FY 2002 and FY 2003?

Mr. Allen: CDC conducted 23 inspections in FY2001. DHHS has arranged for the immediate detail of 2-full time staff from FDA to assist CDC with the current inspection workload. Additionally, CDC is preparing a one year staffing contract for continued assistance with the inspection process and anticipates that all registered facilities will be inspected within that year. This will be followed by a long term staffing contract to provide ongoing support for this area.

Mr. Obey: Is there currently a backlog of applications for registration under the select agent rule pending review? If so, how large is that backlog?

Mr. Allen: CDC has received 40 new applications for registration, 56 requests for amendment to an existing registration, and 103 applications for the renewal of an existing registration that are pending. Recently CDC detailed four employees for 6-8 weeks, to assist in processing these pending requests. In addition, CDC is preparing a one year staffing contract for continued assistance with the application review process. This will be followed by the addition of new FTEs for continued support of these functions.

EDUCATIONAL INCENTIVES FOR CURRICULUM DEVELOPMENT AND TRAINING PROGRAM

Mr. Obey: What are your specific plans for the proposed new "Educational Incentives for Curriculum Development and Training" program? For example, how do you anticipate funding would be divided between training for health professions students and continuing education for practicing health professionals? To what extent would funds be used for curriculum development and to what extent to subsidize actual training? What kinds of institutions would be the grantees? Which health professions would be targeted? What criteria will be used in awarding funds?

Mr. Allen: The goal of this program is the development of a healthcare workforce that possesses the knowledge, skills and abilities to 1) recognize indications of a terrorist event in their patients; 2) treat their patients in a safe and appropriate manner; and 3) rapidly and effectively alert the public health system to such an event at the community, state, and national level. This will be accomplished through the fostering of continuing education and through providing incentives for curricular reform.

We expect that these incentives will be available for both health professions schools and professionals themselves to participate and include mechanisms such as free or low cost continuing education, faculty development and pilot programs for curricular reform.

The disciplines targeted through this program include physicians, dentists, nurses, nurse practitioners, physician assistants, pharmacists, allied and other health personnel. Additionally, the majority of funds will be used for the continuing education of practicing health professionals. It is felt that this allocation of funds will produce the most rapid increase in the Nation's level of preparedness.

Criteria used for awarding funds will include the level of interdisciplinary involvement of the proposal, the experience of the key personnel, the proposed methodology and the demonstration of linkages with other entities involved in preparedness and response activities, including the State Designated Agencies for Emergency Preparedness.

PUBLIC HEALTH TRAINING FACILITIES

Mr. Obey: How would the new HRSA Curriculum Development and Training program differ from existing and proposed efforts at the CDC, including the Centers for Public Health Preparedness, the National Laboratory Training Network, and the Public Health Training Network?

Mr. Allen: HRSA is committed to working with our partners across the Department. HRSA has already shown capability to coordinate activities among internal and external partners to best utilize the available funds. Examples of this can be seen in HRSA's collaboration with the CDC to avoid overlap and duplication of effort in areas where HRSA's Public Health Training Centers and CDC's Centers for Public Health Preparedness exist in the same community. HRSA will continue this level of cooperation and coordination in the future.

This new program will allow HRSA to utilize its extensive network of partners including Academic Health Centers, Community Health Centers, Area Health Education Centers and the National Health Service Corps to prepare health professionals that might not otherwise be reached. HRSA has the experience and contacts necessary to prepare and deliver educational materials in cost-efficient and effective methods. The Educational Incentives for Curriculum Development and Training Program will make a great contribution to the Nation's efforts to prepare for and respond to emerging threats.

HOSPITAL INFRASTRUCTURE PROGRAM

Mr. Obey: What is the difference between the "Hospital Preparedness" program (proposed to be funded at $235 million in FY 2003) and the new "Hospital Infrastructure" program (proposed to receive $283 million in FY2003)?

Mr. Allen: The second year of funding for the Hospital Preparedness program will support continued implementation of State and regional plans to upgrade the ability of hospitals and other health care entities to respond to biological events and to develop a multitiered system in which they (i.e., hospitals, EMS systems, community health centers, poison control centers) are prepared to triage, isolate, treat, stabilize and refer multiple casualties to identified centers of excellence. The Hospital Infrastructure program will focus on funding necessary infrastructure improvements and expansions through three specific objectives: helping hospitals improve their capability to control infection through such means as quarantine and isolation while treating individuals who have or are at risk for a communicable disease; assisting hospitals with the purchase of personal protective equipment; decontamination facilities and other equipment for decontamination of biological agents and ensuring adequate hospital laboratory capacity.

Mr. Obey: Under the new Hospital Infrastructure program, would HRSA provide grants directly to hospitals or would funds be provided to states, territories and large cities for them to distribute to hospitals? How would funds be allocated among the states? Would there be minimum federal criteria for allocating and using funds, or would these decisions be left to each state's plan?

Mr. Allen: Under the Hospital Infrastructure program, HRSA will provide funding to States, territories and large cities for them to distribute to hospitals. The method for distributing funds is still under discussion. Hospital infrastructure applications which are consistent with State preparedness plans will be approved in accordance with a prioritization and funding schedule developed and approved by the State in which the hospital is located. HRSA will require that individual expenditures conform to the intention of the program and will monitor the expenditures as is the case with all other grant programs but otherwise, spending decisions will be those of the States.

Mr. Obey: What requirements and obligations would apply to hospitals receiving funding under the Hospital Preparedness and Hospital Infrastructure programs?

Mr. Allen: Under the Hospital Preparedness Program, the State Health Departments are to target at least 75 percent of the funds to enhance the preparedness of hospitals and other health care entities. Most of the states are building in requirements that participating hospitals will contribute to meeting the overall objectives of the program, sometimes by taking specific actions or by meeting certain standards of readiness. Specific guidance has yet to be written for the Hospital Infrastructure program. Guidance will be developed in conjunction with inclusion of funds in the FY 2003 appropriations bill.

Mr. Obey: The description of the proposed Hospital Infrastructure program in HRSA's budget justifications mentions three areas of emphasis: laboratories, infection control, and decontamination. It does not mention the need for "surge capacity" to treat

large numbers of patients in the event of a major disease outbreak. Would assistance to develop surge capacity be provided through this program, the Hospital Preparedness program, or neither?

Mr. Allen: Assistance to develop surge capacity is covered in the planning for the Hospital Preparedness program under the categories of Patient Transfer and Regional Hospital Plans, which require States to plan regionally for a potential epidemic involving at least 500 patients.

ANTHRAX VACCINE

Mr. Obey: Do you have an estimate of the amount of funding that will ultimately be needed to improve: the preparedness and capacity of hospitals to handle bioterrorist and other mass casualty incidents and major disease outbreaks? If so, what is that estimate?

Mr. Allen: The American Hospital Association estimates that hospitals will need to invest over $10 billion to upgrade hospital facilities' disaster readiness. The $135 million in FY 2002 and the $518 million in the FY 2003 President's Budget are important steps in helping hospitals reach their preparedness.

Mr. Obey: What is the Department's current plan for acquiring, stockpiling, and using anthrax vaccine?

Mr. Allen: The nation has an urgent and compelling need to have a second-generation anthrax vaccine product available as quickly as possible, but at the moment, one must still be developed and tested. Given that the research, development, clinical testing, and procurement of a second-generation anthrax vaccine are very closely linked activities, and given the need to accelerate these efforts, we believe it makes a lot of sense to have all of this carried out in one place through NIH. NIH has been given this task in line with its successful track record in the development and testing of other vaccines. Ultimately, the vaccine, when purchased, will be managed by CDC as part of the national stockpile.

Mr. Obey: The President's budget includes $250 million at NIH for procurement of a new generation of anthrax vaccine. Is this new generation of vaccine anywhere near ready for production? How long is it likely to take to complete development and testing of the new vaccine? When is it likely to be available for use?

Mr. Allen: A promising new generation anthrax vaccine, recombinant protective antigen (rPA), has been under development for several years within the DoD with NIAID support. NIAID recently produced a clinical lot of the vaccine and is collaborating in clinical development of the vaccine. However, additional product development and testing will be required before this promising candidate is ready for production and licensure. NIAID published an RFP on April 22 for work to accelerate

clinical development of a licensable rPA vaccine, a process that should allow production of a product that would be suitable for emergency use under IND in 2004. Production of a fully licensed rPA vaccine will take additional time, depending on the data that are generated in evaluation of the product in clinical trials.

Mr. Obey: In the meantime, do you intend to purchase stocks of anthrax vaccine produced using existing technology?

Mr. Allen: CDC's National Pharmaceutical Stockpile Program has used $3.2 million of the FY 2002 emergency supplemental funds for a procurement of anthrax vaccine manufactured by BioPort. CDC has also signed a memorandum of agreement with the Joint Program Office of Biological Defense to allow CDC to procure additional doses of licensed anthrax vaccine from BioPort that have been manufactured with current technology.

BIOTERRORISM

Mr. Obey: Please summarize the uses being made by NIH of emergency supplemental funds appropriated in PL 107-117 for bioterrorism preparedness and response.

Mr. Allen: The NIH emergency supplemental funds are being used to construct a biosafety level 4 (BSL-4) laboratory at NIAID's Rocky Mountain Laboratory in Montana, support additional physical security measures for personnel and facilities at NIH, and support biodefense research that includes:

- Completed 680-person study that confirmed the current Dryvax smallpox vaccine can be effectively diluted to provide 75 million doses, a five-fold increase over the original 15 million doses;
- Expanding the clinical trials infrastructure to support an increased number of clinical trials including Phase I studies that will begin this summer and fall on Ebola vaccine, second generation Anthrax vaccine, and third generation smallpox vaccine;
- Genomic sequencing that will support comparative studies of different anthrax strains and anthrax isolets from affected patients; and
- Funding over 100 of more than 700 research grant applications received from academia and industry, including small business, in response to several FY 2002 Request for Applications.

BSL-4 LABORATORY AND RELATED INFRASTRUCTURE

Mr. Obey: Of the supplemental funds provided in FY 2002, $70 million were to be used for construction of a BSL-4 laboratory and related infrastructure costs at NIAID. Please describe the nature and purpose of the facility (or facilities) for which these funds are being used, the estimated cost for completion and occupancy, the current stage of planning or construction, and the timetable for completing and occupying the facility.

Mr. Allen: Biosafety level 4 (BSL-4) facilities are designed to handle the most deadly agents and have exceptional engineering controls. BSL-4 facilities are highly specialized and are only operated in a few locations.

A BSL-4 facility is required for work with dangerous and exotic agents which pose a high individual risk of aerosol-transmitted laboratory infections and life-threatening disease. Also, agents with a close or identical antigenic relationship to Biosafety Level 4 agents are handled at this level until sufficient data are obtained either to confirm continued work at this level, or to work with them at a lower biosafety level.

In April 2002, a developer contract was awarded and the design phase is currently underway with an estimated cost of $66.5 million. The construction of the BSL-4 facilities should be completed in spring 2005 and occupied shortly thereafter.

HRSA'S HOSPITAL PREPAREDNESS GUIDELINES

Ms. Pelosi: I continue to hear concerns about the public health system's ability to handle a mass casualty event, especially in terms of adequate staffing. How will the funding that is requested for hospital preparedness and public health communications strengthen the ability of locality to respond to the huge influx of sick and "worried well" that would accompany a bioterrorist attack?

Mr. Allen: One of the three critical benchmarks that the States and municipalities must address prior to receiving the remaining 80 percent of their award states that State health departments must plan for a potential epidemic involving at least 500 patients in each State or region. Furthermore, HRSA's Hospital Preparedness Guidelines require that States develop a plan for assessing the unmet needs the State has in order to be able to implement a hospital and EMS bioterrorism response. Based upon the results of the needs assessment, a timeline addressing further issues is required, including measurable milestones to facilitate accountability.

The needs assessment should address existing local and State communications capabilities available to hospitals and collaborating entities, and the ability of the statewide communication system to respond to overloading of standard telephone, cellular phone and radio communications during a bioterrorist incident resulting in mass casualties.

In addition, States and municipalities have been asked to describe plans for: (1) monitoring all emergency department and outpatient visits, complaints, and diagnosis from a surveillance and detection perspective, and how this will be integrated on the State and national level; (2) how the general public will be educated as to where and when to present to the hospital or to activate EMS (3) public relations to deal with large numbers of patients, worried well, family and friends, and media.

OFFICE OF EMERGENCY PREPAREDNESS

Ms. Pelosi: What role will the Metropolitan Medical Response Systems, Disaster Medical Assistance Teams, and National Disaster Medical Systems funded through the Office of Emergency Preparedness play in this effort?

Mr. Allen: One of the primary purposes of the Metropolitan Medical Response Systems (MMRS) is to improve local health and medical capability to respond effectively to mass casualty events and to assure federal health and medical capability to rapidly augment the state and local response. The MMRS systems are designed to provide initial, on-site response and provide for safe patient transportation to hospital emergency rooms in the event of a terrorist attack. The systems are characterized by specially trained responders; available special pharmaceuticals and decontamination equipment; on-site health care; and enhanced emergency medical transportation and emergency room capabilities. The funding provided by the Office of Emergency

Preparedness (OEP) supports local jurisdictions in the development of plans directed at the early recognition of an event (including a biological event), mass immunization/prophylaxis, mass care, mass fatality management, and environmental surety. The MMRS areas are encouraged to augment their local health systems to plan for the provision of appropriate health services to all those in the affected area who develop symptoms, as well as for those who have been exposed, but who are asymptomatic.

The National Disaster Medical System (NDMS), through its Disaster Medical Assistance Teams (DMATs), National Medical WMD Response Teams (NMRTs), and specialty teams, is prepared to respond to mass casualty disasters of any kind, natural or man-made. The NMRTs were specifically created and designed to allow the teams to be air-lifted within a few hours, and to provide, in hazardous environments, medical services, decontamination services and/or to assist other Federal agencies and local governments in the response to a terrorist event. DMAT's can also respond within hours, and can provide on-scene medical care, triage and other specialty care (including mental health, burn, crush, pediatric and veterinary medical services) in the aftermath of disasters. Most recently, OEP and NDMS have been on deployment since September 11th, providing medical, veterinary medicine and mortuary/identification services in New York City, at the plane crash sites in Pennsylvania, the Pentagon and Queens, New York. In addition, OEP and NDMS assist other federal agencies, including current assistance to the U.S. Department of Agriculture, which is dealing with an outbreak of avian influenza in Virginia.

ENVIRONMENTAL PUBLIC HEALTH TRACKING NETWORK AND CENTERS FOR EXCELLENCE

Ms. Pelosi: I am very interested in developing the capacity of our public health system to track and respond to both chronic and infectious diseases. I have introduced a bill to create a nationwide health tracking network that will identify the links between disease and exposure to environmental toxins, including those associated with bioterrorism. $17.5 million was included in last year's bill for pilot projects to explore the development of such a network. Can you discuss the progress that has been made in creating uniform standards that will enable public health professional to rapidly identify and report a suspected bioterrorism outbreak?

Mr. Allen: Congress has provided $17.5 million in the FY 02 budget for CDC to begin development of a nationwide environmental public health tracking network including the development of environmental health capacity at state and local health departments. The goal of environmental public health tracking is to develop a surveillance system that can integrate environmental hazards data with human exposure and health effects data that have possible links to the environment. This system will allow on-going monitoring and dissemination of information on environmental contaminant levels, health effect trends, facilitate research, and measure the impact of regulatory and prevention strategies. Environmental public health tracking better prepares federal, state, and local agencies to develop and evaluate effective public health action to prevent or control diseases across our nation.

Funded states and Centers for Excellence will be close collaborators in developing/adopting standards for the environmental public health tracking network. Additionally, CDC is developing partnerships with other government agencies, non-governmental organizations, industry, academics and national standards setting organizations to review, adopt or enhance existing data standards and develop new standards specifications, as needed, that will ensure that data on environmental hazards, exposures, and non-infectious diseases can be linked. The National Electronic Disease Surveillance System (NEDSS) at CDC is already working with national standards setting organizations to expand existing standards for public health purposes related to collection of infectious disease data. The Environmental Protection Agency (EPA) is currently developing/adopting standards for the environmental data being included in its National Environmental Information Exchange Network. CDC is currently exploring the compatibility of data integration and standardization efforts underway by CDC for infectious diseases (NEDSS) and the EPA (for hazards) and will build on these efforts for the National Environmental Public Health Tracking Network.

The development of a nationwide environmental public health tracking network with uniform standards provides CDC with an important tool to protect communities. In conjunction with efforts relating to NEDSS and terrorism preparedness, health agencies will have access to baseline information to assist in the detection of sudden disease outbreaks possibly linked to biological, physical, radiation, or chemical terrorism or other public health emergencies. The large bioterrorism state cooperative agreement provided for a significant investment in surveillance and health tracking networks. In the cooperative agreement guidance, state NEDSS coordinators were encouraged to work closely with Bioterrorism coordinators and colleagues in environmental health tracking to accelerate progress to a fully standards based, integrated public health information infra-structure.

Ms. Pelosi: On a related note, I was pleased to see that your request funds all the new infectious disease and environmental health laboratory needs that the CDC has identified. What investments are being made in state and local laboratory capacity?

Mr. Allen: The answer follows:

- *Biological laboratory capacity*: Focus Area C of the FY2002 Supplemental Funds for Public Health Preparedness and Response for Bioterrorism (Biological Laboratory Capacity) will award $142 million. This is for upgrading laboratory capacity in state and local health departments. We expect these public health agencies to utilize these funds to provide for surge capacity, increased staffing and laboratory testing capabilities for all of the Category A and Category B agents within two years.

- *Chemical laboratory capacity*: In FY2002, a total of $7.5 million is targeted at improving state laboratory capacity in five states (California, New York, Michigan, Virginia, and New Mexico). These five states are members of the Chemical Terrorism Laboratory Network (CTLN) and CDC transfers methods to these laboratories to measure chemical agents in blood and urine samples. So far, these laboratories have received analytical methods for the major nerve agents (including sarin gas that was used in Japan in 1995, soman, tabun and VX) and the sulfur mustard agents (generally known as the blistering agents). They are in the process of receiving methods for cyanide based compounds and lewisites.

BIOTERRORISM/FOOD SAFETY

Ms. DeLauro: Mr. Secretary, I think we both share a strong commitment to our nation's food safety. I was pleased to see in the HHS budget this year you will be hiring over 600 inspectors to monitor our food, especially those imported from other countries. Note: In FY02, the FDA's Food Safety budget totaled around $345 million. Does the budget for FY 2003 include an increase for food safety? What will the total budget be for food safety in FY 2003?

Mr. Allen: We estimate that $502.3 million is included in our FY 2003 budget request for food safety. This figure includes microbial safety of foods, chemical safety of foods to include pesticides, dietary supplements, nutrition labeling, BSE funding, and of course, counter terrorism funding.

Ms. DeLauro: As a result of the funding you received in FY 2002 and the increases you're requesting for FY 2003, what percentage of imported foods will be physically inspected by FDA? What would it take to increase import inspections to 10% or 20%?

Mr. Allen: FDA classifies import coverage as a combination of import field examinations and import laboratory analyses, which are both physical evaluations of the product offered for entry. Import coverage is the sum of these two activities as a percent of the number of line entries. Import field exams are physical examinations performed at the entry point. In FY 2001, FDA performed about 12,000 food import field exams and analyzed nearly 15,000 import samples. So for fiscal year 2001, the Agency conducted physical examinations on 0.6 percent of the foods offered for import into this country of the total line entries of 4.6 million. In fiscal year 2002, we will begin to see real gains in our import coverage because of the increased funding. The counter-terrorism funding will permit the field to double the number of import field examinations and increase the number of samples analyzed by nearly 50 percent in FY 2002. Even with the number of food import line entries increasing to 5.1 million, an increase of 10 percent, we will increase the coverage to 0.9 percent. In FY 2003, when the new investigators are more fully trained and the number of food imports is expected to increase to 5.4 million line entries, the number of import field exams will increase to 48,000. Import coverage will then increase to approximately 1.3 percent of the total food entries.

The increase in resources will allow FDA to bolster our Field staff primarily to increase the coverage for imported foods, cosmetics and dietary supplements at more ports of entry with augmented staff at the busiest; conduct foreign inspections plus compliance and laboratory staff and equipment to test and assess the compliance of products to US standards and to detect chemical, biological and or radiological hazards and agents if present. The remaining resources are devoted to domestic activities that cover FDA and state contract coverage of U.S. food firms with the goal of inspection and follow up for all high risk firms once a year; medium risk every other year and low risk every three years.

With respect to the costs of increased import inspections to 10% to 20%, as Dr. Crawford noted when he testified to the appropriations committee, FDA has not conducted the analysis necessary to develop long-range estimates for resource increases.

Ms. DeLauro: How will the FY 2003 budget improve the safety of our domestic food supply? Will the proposed budget increase inspections of domestic firms, particularly high risk firms?

Mr. Allen: It is estimated that the requested FY 2003 funding request will enable FDA and state contractors funded by FDA to conduct approximately 28,000 domestic inspections. In FY 2001, the Agency accomplished approximately 5,300 inspections, or nearly 80 percent of the identified possible inventory of 6,800 high-risk product/process domestic establishments. The number of domestic establishments projected for high risk coverage in the FY 2002 work plan is 7,000. FDA's goal is to inspect 95 percent or 6,650 establishments. This goal includes FDA equivalent inspections performed by the States under contract.

High risk establishments are manufactures, packers/repackers, and warehouses processing products that include: modified atmosphere packaged products, acidified and low acid canned foods, seafood, custard filled bakery products, soft, semi-soft, soft-ripened cheese and cheese products, un-pasteurized juices, sprouts or processed leafy vegetables, fresh vegetables shredded for salads and processed root and tuber vegetables, sandwiches, prepared salads, infant formula, and medical foods.

During the course of this year additional high risk products were identified that had not previously been included in the base FY 2002 high risk inventory. These include establishments that manufacture a product that may contain a commonly allergenic substance (milk, eggs, fish, crustaceans, tree nuts, peanuts or soybeans), and dietary supplements that may contain bovine derived ingredients from countries identified in the USDA regulation (9 CFR 94.18). Some non-high risk inspections have been redirected in FY 2002 to cover these new concerns. Any new establishments identified during the course of completing the work plan, such as a low risk bakery that has been found to produce cookies with nuts, should be added to the list of establishments that will form the high-risk inventory of FY 2003. FDA will continue to evaluate and adjust the definition of high risk establishments.

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, producers and intelligence on anticipated risks to target the products for physical and laboratory examination. It relies on data integrity activities that reduce the opportunity for products to be incorrectly identified at ports. It relies on cooperation from producers so that FDA can identify sources that are unlikely to need physical testing. 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.

The relentless growth in the volume of domestic as well as imported food products, which are increasingly in ready-to-eat-form consumer sale packaging, means that FDA is unlikely to have budget increases to keep pace. Food imports are now growing at 10 percent per year. Historically, FDA import resource budgets have not kept pace. FDA needs to use all the potential tools available to improve confidence in food security and safety.

In short, while we are ramping up our food inspections, we need to inspect smarter, not just more. That is why FDA is making significant investments in technology and information resources. We are using funds to work to further improve targeting and using force multipliers such as IT.

Ms. DeLauro: In your opinion, are the resources you are requesting for food safety adequate to protect our food supply? Are additional funds needed?

Mr. Allen: Resources provided to FDA from FY 1998 to FY 2001 allowed us to make fundamental improvements in food safety, pathogen reduction, and public health. Working together with CDC, USDA, and state and local governments, we now have newer surveillance systems, stronger prevention programs, and faster outbreak response.

The FY 2002 Budget allowed us to build upon this success and expand food safety to cover chemicals and physical contaminants, and improve imports coverage. The FY 2003 budget will allow us to enhance imported food inspections obtained through the FY 2002 Emergency Supplemental funding for Counter Terrorism.

These are only a few of the major activities that FDA has conducted with FY 2001 and FY 2002 funding. With the continued support of the Congress in FY 2002, we anticipate further gains in additional reductions in foodborne illness as well as illness from chemical and pesticide contamination. I would be happy to provide a summary for the record.

In overseeing seafood safety, FDA completed an evaluation of the Seafood HACCP Program for calendars years 1998 and 1999. The evaluation showed substantial progress by the seafood processing industry in implementing the full range of preventive controls that became mandatory in December 1997, as measured against a baseline study performed in 1992. Moreover, in early 2001, FDA issued a "mid-course correction" to focus seafood inspections on those presenting the highest risks to consumers - - i.e., pathogens, histamines, and those firms without HACCP plans.

The National Antimicrobial Resistance Monitoring System, or NARMS, has been expanded to add an animal feed component. This expansion will permit the monitoring of animal feeds for enteric organisms that cause foodborne illness with sampling protocol approval, and a third site for susceptibility testing has been added to handle samples from the retail meat component of the pilot study designed to determine

the prevalence and antimicrobial resistance patterns of foodborne bacteria in commonly consumed meats. Five FoodNet sites will begin to collect retail meat and sent the isolates to the three testing sites for susceptibility testing.

FDA published a final rule "Hazard Analysis and Critical Control Point (HACCP); Procedures for the Safe and Sanitary Processing and Importing of Juice" to ensure the safe and sanitary processing of fruit and vegetable juices by mandating the application of HACCP principles. Implementation began in FY 2002 for the largest firms.

In addition, the Agency has:

- Supported emergency response efforts associated with food outbreaks connected with suspected or actual counter terrorist activities.
- Prepared field staff to safely seize, remove, and dispose of contaminated products by developing procedures and providing appropriate facilities and equipment.
- Published a proposed rule that will require marking, prior to exportation, all imported foods refused admission into the U.S. for safety reasons.
- Designed industry partnerships to assure food safety and supported certification of procedures for the reconditioning of imported spices and sponsored training of industry in product security and safety.
- Awarded Innovative Food Safety Grants to 13 State and local regulatory agencies in the amount of $505,000.
- Awarded 38 State food contracts for over 6,443 food inspections costing a total of $3,450,000.
- Published the Vibrio parahaemolyticus risk assessment and worked with the Interstate Shell Sanitation Conference (ISSC) on control plan implementation.
- Published, jointly with the United States Department of Agriculture, a draft risk assessment on Listeria monocytogenes contamination in food, and convened a public meeting to solicit comments on the draft risk assessment and draft action plan.
- Finalized a Listeria control and interventions research plan.
- Distributed a senior citizen food safety video and 25 publications as a package to 800 offices of the Administration on Aging, 10,000 senior day care centers and all county and State Extension Service offices.
- Created and distributed Science and Our Food Supply, in collaboration with the National Science Teachers Association, an innovative, interactive supplementary curriculum for use in middle level and high school science classes in the United States.
- Oversaw the development of eLEXNET, the nation's first seamless data exchange system for food safety testing information, and facilitated data exchange between local, state, and federal agencies.

Specifically, in the area of research, FDA continued or initiated the following:

- Studies that indicate that poultry products may serve as reservoirs of fluoroquinolone-resistant campylobacter spp;
- Research that indicates that FDA may need to standardize the identification techniques used to characterize the components of competitive exclusion products used to pre-infect chickens, preventing adverse bacterial infections;
- Research on bacteria contained in commercial competitive exclusion products that contain vancomycin-resistant genes;
- Statistical models for microbial risk assessment submitted for publication;
- A quantitative risk assessment that modeled the human health impact of fluoroquinolone-resistant campylobacter infections associated with consumption of chicken. The risk assessment showed that development of resistance in food-producing animals has an impact on human health by compromising the effectiveness of human medicines.
- Research on dose-response modeling of microbial risk assessment;
- Measurement of the effect of low level antibiotic residues on the human intestinal flora; and
- A protocol to examine probiotic (viable bacterial cultures that are beneficial to the host) effects on the host organism's defenses.

In FY 2002, we will continue or initiate the following research projects:

- Risk-ranking framework to evaluate potential high threat microbiological agents, toxins and chemicals in food;
- Research on the practical application of laboratory based biosensor detection technology to detect and analyze microbiological agents, food allergens, toxins, and other bioactive compounds in foods, food additives, and dietary supplements;
- Research on the detection of selected chemical agents used as adulterants in foods, food additives, and dietary supplements;
- Evaluation of the efficacy of multiple heat treatments used during the production of dairy products relative to the inactivation of bacterial spores;
- Analytical methods for rapid detection of microbial threat agents in food; and,
- Development of a bioinfomatic approach to identify the potential allergenicity of food proteins.

The FY 2003 President's Budget addresses these research needs:

- Development of diagnostic tests to produce tools that are needed for field and import examinations to determine if a product has been tampered with or is otherwise tainted;
- Research on Bovine Spongiform Encephalopathy (BSE) decontamination/deactivation procedures;
- Research on BSE recovery/identification methods from foods/cosmetics;

- Research on the risk factors and mechanisms for Chronic Waste Disease (CWD) which affects elk, deer and other domestic game/pen-reared animals; and,
- Analytical methods to detect the presence of prohibited animal substances that could be introduced into the U.S. animal feed supplies by bioterrorists.

SINGLE FOOD AGENCY

Ms. DeLauro: As you may know, last year I introduced legislation to create a single, consolidated Food Safety Administration. I strongly believe that it is critical that we have a seamless, united approach to ensure the safety of our food. Both President Bush and Homeland Security Director Ridge have at the very least encouraged taking a look at creating a single food agency. Do you think a single food agency will improve the safety of our food supply? Would you support commissioning a study that would do an analysis of alternative food safety structures, including a single food agency?

Mr. Allen: Today, almost everyone says that if you had to start out de novo with a new food safety system, you would have it in one Agency. We did start out de novo at one point and all of it was in the Department of Agriculture. Over time, for various reasons, many of those areas have been spun off. The FDA was spun off in the 1940s, ending up in what became the Department of Health Education and Welfare, now the Department of Health and Human Services. The Environmental Protection Agency didn't leave until the 1970s and then as a separate Agency entirely.

Our goal is to have a fully integrated food safety system that ensures American people are getting the maximum public health protection possible. Whatever the structure of our food safety system, our first concern is how well it functions.

We need to look critically at the existing system and determine where improvements in both efficiency and effectiveness can be made. There are many approaches to improving the system, with consolidation of food safety functions into a single agency being only one option. We need to look closely at the pros and cons of any significant consolidation or realignment of agency functions.

Any proposals must also take into account the new food safety requirements developed by the Administration and included in bioterrorism legislation. The Bioterrorism Preparedness Act and the Public Health Security and Bioterrorism Response Act have passed the Senate and House respectively and Congress is expected to complete the conference process soon. The legislation requires HHS and USDA to undertake significant new actions to improve our ability to prevent, identify and respond to an bioterrorist attack or natural outbreak of foodborne illness.

The President's Council on Food Safety was established under the last administration, took some significant steps in the coordination of food safety activities across the federal government. The Council also had its critics, claiming it was ineffective in stimulating any significant food safety reform. We are looking at the lessons learned through the work of the Council to determine how best to move forward.

Even though the American food supply is viewed widely as one of the best in the world, the CDC estimates that there are still 76 million cases of foodborne illnesses in the U.S. each year. Clearly there is more work to be done.

The Congress could immediately make the current food safety system stronger by completing the bioterrorism conference committee process and passing the Administration's food safety proposals. As you know, this legislation would give the Administration many new food safety tools including registration, record keeping requirements, administrative detention, debarment, and increased coordination of food safety activities between the executive branch agencies.

In response to the ongoing threat of bioterrorism and the millions of annual cases of naturally occurring foodborne illness, the Administration will continue to evaluate the current system and identify steps to improve the efficiency and effectiveness of the system.

HOSPITAL PREPAREDNESS PROGRAM

Ms. DeLauro: Can you give us some details about HRSA's Hospital Preparedness program and how you are working with hospitals to help them prepare for future incidents? How are you training medical providers to ensure that they are prepared to recognize the signs of bioterrorist attacks?

Mr. Allen: The purpose of this new Bioterrorism Hospital Preparedness cooperative agreement program is to upgrade the preparedness of the Nation's hospitals and collaborating entities to respond to bioterrorism. This will also allow the health care system to become more prepared to deal with nonterrorist epidemics of rare diseases.

The Health Resources and Services Administration (HRSA) has announced that approximately $125 million is available in fiscal year 2002 for cooperative agreements with 59 State, territorial and selected municipal offices of public health. These awards are for the development and implementation of regional plans to improve the capacity of hospitals, their emergency departments, outpatient centers, EMS systems and other collaborating health care entities for responding to incidents requiring mass immunization, treatment, isolation and quarantine in the aftermath of bioterrorism or other outbreaks of infectious disease.

The cooperative agreements will cover two phases:

- *Phase 1 (Needs Assessment, Planning and Initial Implementation)*: This will consist of State, territorial, regional and municipal efforts to involve entities such as hospital associations, emergency medical systems, emergency management agencies, rural health offices, primary care associations, and VA and military hospitals in a needs assessment of hospital preparedness to respond to a bioterrorist incident, and to develop a plan of action in response to the identified needs.

- *Phase 2 (Implementation)*: States will be given the flexibility to prioritize funding for specific activities based upon their needs assessment. This implementation phase should result in States being able to upgrade the ability of hospitals and other health care entities to respond to biological events, to develop a multitiered system in which local health care entities are prepared to triage, isolate, treat, stabilize and refer multiple casualties of a bioterrorist incident to identified centers of excellence, or to develop multistate or regional consortia to pool limited funding to accomplish these goals. State health departments will be required to allocate most of the Phase 2 funds to hospitals. To the extent justified, a portion of these funds could be made available to collaborating entities that improve hospital preparedness.

Awards are being made in two phases. Phase 1 has been funded at 20 percent of the total (approximately $25 million), and is intended to support the State's efforts to complete a needs assessment, to develop a plan of action, and to begin initial implementation efforts. Phase 2, funded at 80 percent of the total (approximately $100 million), will be awarded for implementation efforts, provided the implementation plan is approved by DHHS. The State Health Departments are required to distribute at least 75 percent of the total hospital preparedness award to hospitals and collaborating health care entities to upgrade their ability to respond to bioterrorist events.

With regard to training, the guidance does include an outline for developing state-level training programs for clinicians in hospitals and supporting entities (health centers, EMS units, poison control centers) to recognize and treat infectious diseases that might occur through bioterrorist means. The Hospital Preparedness program also has a technical assistance center under contract. One of their charges is to accumulate, evaluate and disseminate training resources to grass-roots level clinicians and state health department grantees.

The President's FY 2003 budget also includes $60 million for a new Educational Incentives for Curriculum Development and Training program focused on Bioterrorism.

PUBLIC AND PRIVATE LABORATORIES

Ms. DeLauro: Earlier this year, I visited a lab at Yale University where they are conducting important research on how to diagnose and treat anthrax. Can you tell us what, if any, support you are giving to private laboratories like this? What steps are you taking to improve communication between public and private labs so that researchers can share information and work together?

Mr. Allen: NIH spends approximately 85 percent of its total budget in support of biomedical and behavioral research and research training by more than 50,000 scientists located at more than 1,700 universities, research institutions, and medical centers across the United States and abroad, including Yale University. NIAID is the primary NIH

Institute that supports and conducts research on the diagnosis, prevention, and treatment of infections caused by a wide variety of emerging pathogens, including agents that could be intentionally introduced.

NIAID has several mechanisms to encourage communication and partnerships between universities, medical centers, and private industry in conducting biodefense research. One example is the recently announced initiative, "Partnerships for Novel Therapeutic, Diagnostic and Vector Control Strategies in Infectious Diseases." This initiative encourages collaborations between industry and academia in areas that are traditionally not a high priority for industry. In addition, a number of the new initiatives to be announced in the next six months strongly encourage collaborations among a variety of scientific disciplines and between industry, academia and federal organizations.

Ms. DeLauro: How much of the Presidents budget is devoted to bioterrorism preparedness training specifically for emergency physicians?

Mr. Allen: The President's 2003 budget requests $60 million for health professions training. The proposed funding is not allocated to specific health professionals, but is directed at the full range of professionals who might be expected to deal with a bioterrorist event or mass casualty situation. As critical elements of a bioterrorism response, emergency physicians and other health care providers would be generally eligible for training under this new program. They could also participate in training funded by the States under the Hospital Preparedness Program.

In addition, CDC's request for State and local capacity funding anticipates an expanded focus on cooperative training between public health agencies and local hospitals for education and training of key public health professionals, infectious disease specialists, emergency department personnel, and other healthcare providers in preparedness for and response to bioterrorism, other infectious disease outbreaks, and other public health threats and emergencies.

Ms. DeLauro: Does either of the definitions of "front-line responder" or "first-responder" include emergency physicians? If not, why not?

Mr. Allen: Under HRSA's Hospital Preparedness Program, the term "front line responder" would include the entire range of health and safety personnel, including emergency physicians, who are expected to respond to any casualty event, either isolated or involving mass destruction.

Ms. DeLauro: There are 35,000 active practicing emergency physicians in the United States today. All of these physicians receive additional training continued education or CE. Does any of the presidents budget devote money to training through this process?

Mr. Allen: Under the proposed program of Educational Incentives for Curriculum Development and Training (proposed at $60 million in FY 2003), grants will be made to health professional educational programs to train students at the undergraduate and graduate levels and to provide continuing education to practicing providers to be prepared to recognize and manage bioterrorist events and mass casualty situations.

The HRSA's 2002 Bioterrorism Hospital Preparedness Program guidance also identifies training as an eligible cost. To that end, all hospital based and prehospital providers would be eligible to participate in training under this grant. There is maximum flexibility in decisions made at the State level on the use of these funds. Thus, specific health care providers would be eligible at the State's discretion.

HRSA anticipates preparing program guidance for 2003 both for Hospital Preparedness and for Curriculum Development and Training, subject to Congressional appropriations. In these guidance, HRSA anticipates describing training programs which would include continuing medical education credit for medical, nursing and other health professionals.

Ms. DeLauro: How many dollars do you believe should be devoted to training emergency physicians for bioterrorism preparedness training?

Mr. Allen: The President's Budget has requested $60 million in FY 2003 to initiate a program of curriculum development, training and continuing education. Since much of the training will be multi-disciplinary, costs are not broken out by specific types of health professionals. Under the Hospital Preparedness program, allocations for training needs for specific health care providers are at the discretion of the 59 different state, territorial or municipal entities.

WEDNESDAY, MARCH 13, 2002.

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. RUTH L. KIRSCHSTEIN, M.D., ACTING DIRECTOR, NIH
WENDY BALDWIN, DEPUTY DIRECTOR FOR EXTRAMURAL RESEARCH
MICHAEL GOTTESMAN, DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH
CHARLES LEASURE, DEPUTY DIRECTOR FOR MANAGEMENT
WILLIAM BELDON, DEPARTMENT OF HEALTH AND HUMAN SERVICES
ANDREW VON ESCHENBACH, DIRECTOR, NATIONAL CANCER INSTITUTE
CLAUDE LENFANT, DIRECTOR, NATIONAL HEART, LUNG AND BLOOD INSTITUTE
LAWRENCE A. TABAK, DIRECTOR, NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH
ALLEN M. SPIEGEL, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
AUDREY S. PENN, ACTING DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE
ANTHONY S. FAUCI, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
MARVIN CASSMAN, DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
DUANE ALEXANDER, DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
PAUL A. SIEVING, DIRECTOR, NATIONAL EYE INSTITUTE
KENNETH OLDEN, DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
RICHARD J. HODES, DIRECTOR, NATIONAL INSTITUTE ON AGING
STEPHEN I. KATZ, DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES
JAMES F. BATTEY, JR., DIRECTOR, NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS
RICHARD NAKAMURA, ACTING DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH
GLEN R. HANSON, ACTING DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE
RAYNARD KINGTON, ACTING DIRECTOR, NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM
PATRICIA A. GRADY, DIRECTOR, NATIONAL INSTITUTE OF NURSING RESEARCH
DONNA DEAN, ACTING DIRECTOR, NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING
JUDITH L. VAITUKAITIS, DIRECTOR, NATIONAL CENTER FOR RESEARCH RESOURCES
STEPHEN E. STRAUS, DIRECTOR, NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE
JOHN RUFFIN, DIRECTOR, NATIONAL CENTER ON MINORITY HEALTH AND HEALTH DISPARITIES

GERALD T. KEUSCH, DIRECTOR, FOGARTY INTERNATIONAL CENTER
DONALD A.B. LINDBERG, DIRECTOR, NATIONAL LIBRARY OF MEDICINE
YVONNE T. MADDOX, ACTING DEPUTY DIRECTOR, OFFICE OF THE DIRECTOR
JACK WHITESCARVER, ACTING DIRECTOR, OFFICE OF AIDS RESEARCH
STEPHEN A. FICCA, ASSOCIATE DIRECTOR FOR RESEARCH SERVICES
SUSAN QUANTIUS, ASSOCIATE DIRECTOR FOR BUDGET
KERRY WEEMS, ACTING DEPUTY ASSISTANT FOR BUDGET, DHHS

Mr. REGULA. Okay, we will get started. We are happy to welcome the NIH team here this morning. On behalf of all the people of America, we are especially pleased to welcome you, because they depend on you a great deal for their well being in the future.

Dr. Kirschstein, if I believe the press reports, this may be your last appearance before this Committee—not your last appearance, but before this Committee. [Laughter.]

Have to be careful with the semantics here.

I just want to express the appreciation of millions of Americans for your wonderful service at NIH. You and your husband have been dedicated Americans, 46 years I believe that you've been out there. Think of the millions of lives that have been improved because you have done, both as a researcher and a leader, you have touched their lives.

I told the Committee last year when we started, I said, the Bible says there are two great commandments, love the Lord and love your neighbor. This is the love your neighbor Committee. We love our neighbors through the activities of institutions like NIH. As I understand it, there were nine institutes and it's under $100 million when you came there. That's why they call them the good old days. [Laughter.]

Today there are 27 institutes and $23 billion appropriations. Not many that can lay claim to that many years of really great service to the people of this Nation. I just think it is wonderful what you have been able to do. We will miss you whenever you decide you will leave out there, and we certainly wish you well in everything you do. What you leave in this world are few things, legacies. I have an interesting thing happening in our office, and I am sure David, you and Roger have the same thing, that is veterans of World War II want their medals. They write to us and ask, will you get my medals. When they left the service, they did not want any part of it. Now suddenly they are getting closer to the end and they want their grandchildren to have their medals.

We all like a legacy. You have been especially blessed, because you have had an opportunity to leave a great legacy. It must make you feel very good to be able to do that.

Dr. KIRSCHSTEIN. Thank you. I appreciate everything you have said.

Mr. REGULA. Mr. Obey, would you like to make some comments?

Mr. OBEY. I understand you've been maligning the past? [Laughter.]

Mr. REGULA. When it was a $100 million budget for NIH, you cannot malign it.

Mr. OBEY. Amen.

Let me simply say, Dr. Kirschstein, that I think you are a precious national asset. I do not think very many people understand what NIH is. They certainly do not in my district. Yet, they all understand what medical research is all about and they understand what medical progress is all about.

I think your career has been really remarkable. There are a lot of people in Congress and in this town in other capacities who get a lot of attention and a lot of press. And there are a lot of other people in those same institutions who do a lot of the work and solve a lot of the problems. You fall in that latter category in my book.

You have now been what, twice acting director of the NIH?

Dr. KIRSCHSTEIN. Yes, sir.

Mr. OBEY. And in my view, despite your indication that you are not interested in being the permanent director, I think any President would have been smart to nominate you any time there was an opening to run that shop.

But I also want to mention the almost 20 years that you spent running the Institute of General Medical Sciences. You know, there was a time when it looked like people were going to earmark funds for this disease or that disease, people posing for holy pictures, trying to show who was most against cancer and most against heart disease or most against diabetes or some other disease, so they wanted to earmark funds for the Cancer Institute, for the Heart Institute. But nobody ever wanted to earmark funds for the General Medical Sciences Institute, because who the hell ever died of general medical——

[Laughter.]

Mr. OBEY. It was tough to get people to understand that a lot of the very basic research took place at that Institute. But you have served that institution so very well, and you have served the country so very well. The public, even though 99 percent of them will never know your name, have all benefitted from your service. I know I am grateful, and if they knew about it, they would be, too.

Dr. KIRSCHSTEIN. Thank you very much, Mr. Obey.

Mr. REGULA. Mr. Wicker, do you want to make a brief comment here?

Mr. WICKER. I think I will wait for questions.

Mr. REGULA. Okay. You'll be number one.

Steny.

Mr. HOYER. Thank you very much, Mr. Chairman.

For those of us who have served on this Committee for a number of years, Dr. Kirschstein, and frankly all the directors of the Institute, but Dr. Kirschstein has been an extraordinary asset, as David Obey said. Mr. Chairman, I missed most of your comments. Sorry for being late.

But she is and has been a national asset. More than that, she has been a personal asset, I think, for each of us on the Committee. Always open to answer questions, to work with us on problems that we had in figuring out what we needed to be doing, working with us on the political problems that confront a committee like this, as Mr. Obey mentioned, where there is the inclination to want to earmark and to focus on a particular disease or ailment research project.

And that is a real asset for NIH, I think. So many of the directors have that same skill, which I think their medical colleagues may not appreciate as much as they appreciate their intellectual and professional skills, which are obviously very, very high. But I wanted to join both Mr. Regula and Mr. Obey. Frankly, our Chairman has not had as long an experience, he is by the way, doing an outstanding job chairing this Committee, and we're very lucky to have him. And of course, he's had very long experience on the full Committee.

But I know Mr. Obey and I, I suppose, have been on this Committee longer than anybody else on the Committee. Both of us consider Dr. Kirschstein to be one of the extraordinary talents of the Federal Government and of our country. We thank her for her service.

Dr. KIRSCHSTEIN. Thank you, Mr. Hoyer.

Mr. REGULA. Mr. Miller.

Mr. MILLER. Let me make a brief comment, echoing the comments of my colleagues. We were fortunate for over two years to be without a director that you were able to step in with the depth of knowledge and experience there, but also your husband. He stepped in at the Cancer Institute and did a very fine job. It's always difficult to take an acting position, because you do not have the complete command of everything. During these times of great growth in the budget, you both have done a good job. Your husband has done a good job, too.

Dr. KIRSCHSTEIN. Thank you.

Mr. HOYER. I know the gentleman didn't mean that. We've had a director. It's had "acting" in front of her name. But that didn't, in my opinion, make any difference, either how the, and to the credit of the Institute directors, how they responded to her leadership or the leader, the quality of the leadership she gave.

I know you didn't mean that, but——

Mr. MILLER. It makes it a more difficult challenge when you have acting in front of your name.

Mr. HOYER. It does make a difference, but she did an extraordinary job.

OPENING REMARKS

Mr. REGULA. Okay. We look forward to hearing from you and your testimony. We will make the entire testimony a matter of record, in the record, and if you'll summarize, we will appreciate it. Again, welcome, and thank you on behalf of America.

Dr. KIRSCHSTEIN. Thank you very much, Mr. Regula. I am overwhelmed, and hope I can perform again for this time.

Let me introduce the people at the table. To my left is the Acting Deputy Director of NIH, who has done an extraordinary job of helping me through these two plus years, Dr. Yvonne Maddox. To her left is Dr. Wendy Baldwin, who is the Deputy Director for Extramural Research, and to her left, Dr. Michael Gottesman, the Deputy Director for Intramural Research.

To my immediate right is Ms. Sue Quantius, who I think almost needs no introduction to the members of this Committee and who is currently the Director of the Office of Budget. We want to welcome to the table for the first time Mr. Charles Leasure, who is the

Deputy Director for Management and immediately to his right is Mr. William Beldon from the Department.

With that, Mr. Chairman, I want to tell you how very honored I am to appear before the Committee and to represent the 27 directors, colleagues without whom I could have not done the job, the directors of the 27 institutes and centers, each of whom has presented to you a written statement related to the President's budget proposal for fiscal year 2003. I shall now present the overview of the total Administration budget for the National Institutes of Health for 2003.

The Congress, the Administration and the American public have been committed to doubling the funding of NIH by the end of 2003. Although scientific accomplishments often take years to produce new treatments or diagnoses, a confluence of the generous budgets and the extraordinary scientific opportunities has already begun to yield amazing results. The current budget proposal is $27.3 billion, an increase of 15.7 percent over fiscal year 2002. It completes the original commitment, enables the NIH to continue to take advantage of the broader and deeper opportunities now at hand to understand diseases and to improve health, and it opens the way for future progress in medical research.

Opportunities truly are at hand. Some of them are general, benefiting research in many areas, and others are specific and deal with particular diseases and disorders. Among the general opportunities the complete draft of the DNA sequence of the human genome is the best known of the new tools. It is helping scientists in so many ways from so many disciplines to understand how the human body works and what causes disease.

But there are several other areas of investigation that are changing the way biomedical research is being done. They include proteomics, the computer-aided analysis of the patterns present in large sets of proteins, proteins being the products of our genes. They will help with the goal of understanding the function of those proteins.

They include combinatorial chemistry, a new way to generate large libraries of molecules that can be screened for use as drugs. And they include new, advanced imaging techniques that enable scientists to see not only within the human body but within its cells as various functions are being carried out.

There are of course new and expanded opportunities in therapeutics and prevention that we will be undertaking. These efforts do not eclipse the research in specific diseases and disorders, but actually complement them and enable us to acquire new knowledge to more fully understand and ultimately to control or defeat cancer, Parkinson's disease, diabetes, Alzheimer's, asthma, heart disease and many, many others, as well as to prepare for incidents of bioterrorism. The President's budget for 2003 provides the NIH and its institutes and centers with funding to deliver the results on these promises.

Mr. Chairman, my written statement has a number of important examples of NIH's accomplishments, many of which will be discussed over the next several days, particularly regarding cancer, Parkinson's and Alzheimer's disease. But there are so many others that I want to highlight a few new ones.

For example, we used to think that the heart muscle, damaged as a result of heart attack, could not be repaired. But recent studies have shown that heart cells can indeed regenerate and if the proper materials and sustenance are given to them, they can be stimulated to regenerate. This repair process can be enhanced, thus increasing not only survival but the health of the previously damaged heart.

The area of fundamental research, solving the three dimensional structures of essential molecules, is very important. After 20 years of work, scientists have determined the structure of an enzyme which is responsible for the first step in making the building blocks of life, proteins. This structure suggests that each and every one of its dozen sub-units must properly fit together so that such proteins can be made.

Understanding how this fit occurs and how it differs between lower organisms such as bacteria and humans may allow a very practical approach to the design of antibiotics specifically tailored to those bacteria, helping us with infections.

We have learned an enormous amount from genome sequencing. We have learned that the genetic sequence between any two people is about 99.9 or more percent the same. But we do know that in common diseases, among them asthma, there are complex interactions between multiple genes as well as other factors such as the environment. Genetic links associated with asthma are now found in chromosomes 5, 8, 12, 14 and 15.

But in addition, linkage to a gene on chromosome 11 is unique in African-Americans, while genes on chromosome 1 and 6 are unique in Hispanics and whites. Since minority populations have substantially higher rates of hospital admissions and emergency room visits associated with asthma, identifying such genetic factors, even if they each have a small effect, may improve therapeutic options for all patients.

I have presented, therefore, in my written and verbal statements, a brief summary of the scientific areas we are studying. Our research portfolio is so broad, so deep and so complex, that even if I went on for a long time, I would not be able to give you a complete picture. Yet I am confident that the fiscal year 2003 budget request enables NIH to sustain the momentum of research already in progress, to open the way to new research opportunities in the coming fiscal year and the years to come, and to augment both our research infrastructure and our human capital.

Some practical things about the fiscal year 2003 budget: The request would fund a total of 9,854 new and competing research grants and a total of all research grants of 38,038, the highest annual total ever. The intramural research program increases by 15 percent over the 2002 estimate, and most institutes and centers will increase by 9 percent while the National Institute of Allergy and Infectious Diseases and the National Cancer Institute increase by 62 percent and 11 percent respectively, as a result of the large increases in bioterrorism and cancer research.

The research management and support, RM&S funds, are vital if the NIH is to manage its programs and resources efficiently and effectively. These funds are used by the NIH to sustain, guide and monitor the extramural and intramural research activities. The

funding increase is about 17 percent in total. Several of the institutes are higher than that because of new responsibilities.

Mr. Chairman, I am sure that you will recall that at these hearings last year, I promised to provide you with an update on the Clinical Research Center construction project. At that time, I apprised you of the fact that the General Services Administration, as the contracting agent for NIH, and in consultation with the Office of the General Counsel, Department of Health and Human Services, had decided to terminate the contract with the then-construction manager of the project, due to certain unresolved issues that had occurred between that contractor and the development manager.

I can tell you now that we have selected a new construction manager, which has recently presented to us a proposed guaranteed maximum price. This price is a great deal more than was expected to complete the building. We are working with the Department and OMB to validate both the GMP and a new schedule and having discussions with all the appropriate parties regarding budget options for covering the additional costs.

Mr. Chairman, this concludes my opening statement. I and my colleagues will be pleased to respond to any questions.

[The prepared statement of Dr. Kirschstein follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Ruth L. Kirschstein, M.D., Acting Director, NIH
Statement to the House Subcommittee on Labor-HHS-Education Appropriations
March 13, 2002

on the FY 2003 President's Budget Request
accompanied by

Dr. Andrew von Eschenbach, Director, National Cancer Institute
Dr. Claude Lenfant, Director, National Heart, Lung, and Blood Institute
Dr. Lawrence A. Tabak, Director, National Institute of Dental and Craniofacial Research
Dr. Allen M. Spiegel, National Institute of Diabetes and Digestive and Kidney Diseases
Dr. Audrey S. Penn, Acting Director, National Institute of Neurological Disorders and Stroke
Dr. Anthony S. Fauci, Director, National Institute of Allergy and Infectious Diseases
Dr. Marvin Cassman, Director, National Institute of General Medical Sciences
Dr. Duane Alexander, Director, National Institute of Child Health and Human Development
Dr. Paul A. Sieving, Director, National Eye Institute
Dr. Kenneth Olden, Director, National Institute of Environmental Health Sciences
Dr. Richard J. Hodes, Director, National Institute on Aging
Dr. Stephen I. Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases
Dr. James F. Battey, Jr., Director, National Institute on Deafness and Other Communication Disorders
Dr. Richard Nakamura, Acting Director, National Institute of Mental Health
Dr. Glen R. Hanson, Acting Director, National Institute on Drug Abuse
Dr. Raynard Kington, Acting Director, National Institute on Alcohol Abuse and Alcoholism
Dr. Patricia A. Grady, Director, National Institute of Nursing Research
Dr. Donna Dean, Acting Director, National Institute of Biomedical Imaging and Bioengineering
Dr. Judith L. Vaitukaitis, Director, National Center for Research Resources
Dr. Stephen E. Straus, Director, National Center for Complementary and Alternative Medicine
Dr. John Ruffin, Director, National Center on Minority Health and Health Disparities
Dr. Gerald T. Keusch, Director, Fogarty International Center
Dr. Donald A. B. Lindberg, Director, National Library of Medicine
Dr. Yvonne T. Maddox, Acting Deputy Director, Office of the Director
Dr. Jack Whitescarver, Acting Director, Office of AIDS Research
Mr. Stephen A. Ficca, Associate Director for Research Services
Ms. Susan Quantius, Associate Director for Budget
Mr. Kerry Weems, Acting Deputy Assistant Secretary for Budget, DHHS

Mr. Chairman and Members of the Committee:

I am Ruth Kirschstein, the Acting Director of the National Institutes of Health. I am honored to appear before the Subcommittee, representing my colleagues, the Directors of the 27 Institutes and Centers, each of whom has presented a written statement related to the President's budget proposal for FY 2003. I shall present an overview of the total Administration budget for the NIH for FY 2003.

The Congress, the Administration, and the American public have been committed to doubling the funding of the NIH by FY 2003. Although scientific accomplishments often take years to produce new treatments or diagnostic tools, the confluence of generous Budgets and extraordinary scientific opportunity has already begun to yield amazing results. The current budget proposal of $27.3 billion, an increase of 15.7 percent over FY 2002, completes the original commitment, enables the NIH to continue to take advantage of the broader and deeper opportunities now at hand to understand diseases and improve health, and opens the way for future progress in medical research.

Opportunities truly are at hand. Some are general, benefitting research in many areas, and others are specific, dealing with particular diseases and disorders. Among the general opportunities, the complete draft of the DNA sequence of the human genome is the best known of the new tools, helping scientists in many disciplines to understand how the human body works and what causes disease. But there are several other areas of investigation that are changing the way biomedical research is done. These include proteomics—the computer-aided analysis of the patterns present in large sets of proteins (the products of our genes) with the goal of understanding their function; combinatorial chemistry—a new way to generate large libraries of molecules that can be screened for use as drugs; and new, advanced imaging techniques that enable scientists to see within the human body and within its cells as various functions are carried out. There are, as well, new and expanded opportunities in therapeutics and prevention that we will be undertaking. These efforts do not eclipse research into specific diseases and disorders, but enable us to acquire new knowledge to more fully understand—and ultimately to control or defeat—cancer, Parkinson's disease, diabetes, Alzheimer's disease, asthma, and many other diseases, and prepare for incidents of bioterrorism. The President's budget for FY 2003 provides the NIH and its Institutes and Centers with funding to deliver results on these promises, some of which I will now describe.

CANCER RESEARCH

The FY 2003 budget request provides an estimated $5.5 billion in cancer-related research. By building upon past successes, we will accelerate the pace of cancer research and improve our ability to find better ways to help those whose lives are touched by cancer.

Last month, for example, scientists from the National Cancer Institute (NCI) and the Food and Drug Administration (FDA) reported using proteins found in blood serum to detect cancer of the ovary, even at early stages. This new diagnostic method, built on the concept of proteomics, has great promise. Usually patients with ovarian cancer are diagnosed at a late stage and have only a 20 percent chance, or even less, of survival after five years. Preliminary studies of this new test are able to identify correctly, in a small number of patients, all of those with ovarian cancer who were at stage I of the disease. Not only is this test simple and accurate, requiring only a blood sample, but the approach has exciting potential for diagnosing many other cancers, as well as other diseases.

Last May, as discussed at last year's hearings, another new concept—the design of drugs based on understanding the molecular anatomy of tumor cells—produced Gleevec, which is taken as a pill to treat a chronic type of leukemia that usually strikes middle-aged or older people. While studies continue with Gleevec in patients with this type of leukemia, it is also being tested for those with other cancers, including those that attack the brain and nervous system, the soft-tissues such as muscle, and the gastrointestinal tract. An intensive effort is now underway to identify other cancer-causing proteins in other tumors so that drugs can be specifically designed to block their action.

With the increases requested for FY 2003, the NIH will provide support to answer critical questions about controlling, preventing and screening for cancer. For example, the NIH will conduct the largest prevention study ever to determine if vitamin E and selenium can protect against prostate cancer. The study will include 32,400 men recruited through more than 400 sites in the United States, Puerto Rico, and Canada and is expected to take 12 years to complete. The NIH will also launch the first multicenter study to compare digital mammography to standard mammography for the detection of breast cancer. Digital mammographic technology provides images at higher resolution than standard mammography, and investigators want to determine if it can detect breast cancer more accurately.

These are just a few examples of compelling new avenues for cancer research. While increases for the National Cancer Institute constitute over 80 percent of the proposed increase for cancer research, many other NIH Institutes and Centers will also contribute to the emphasis placed on cancer. For example, the National Center for Complementary and Alternative Medicine will study the integration of complementary and alternative therapies into more conventional treatments for cancer, the National Institute of Neurological Disorders and Stroke will emphasize sophisticated ways to improve the treatment of brain tumors, and the National Institute on Deafness and Other Communication Disorders will continue its research on new therapies to treat patients with head and neck cancers, while preserving their ability to speak.

BIOTERRORISM RESEARCH

The threat of bioterrorism became a reality for the United States with the intentional delivery of anthrax spores through the mail, demonstrating our vulnerability and giving impetus to research to protect the public health. A number of government agencies have specific roles to play in protecting the public from bioterrorism; the role of the NIH is to conduct research to learn more about the viruses and bacteria that can be used in bioterrorism and about how the body responds to such assaults, and to develop counter-measures, such as diagnostic tests, vaccines, and treatments.

The FY 2003 budget request for bioterrorism-related research is $1.75 billion, an increase of $1.47 billion over FY 2002. Most of these funds will go to the National Institute of Allergy and Infectious Diseases (NIAID), which already has a remarkable track record for success in this area of science. For example, in November 2001, scientists funded by the NIAID reported a new understanding about the toxins released by the anthrax bacterium, providing leads for potential new therapies. The NIAID is now completing a study aimed at learning whether use of the current smallpox vaccine, if diluted to stretch the existing supply, could still convey protection; results are scheduled to be reported soon. Meanwhile, the NIAID continues to work on a new, safer smallpox vaccine as well as a new vaccine to protect against anthrax. In addition, members of the NIAID intramural research program have demonstrated the efficacy of an Ebola vaccine in a monkey model. This vaccine will soon enter early safety trials in humans. And as we all remember, Mr. Chairman, when HIV/AIDS was first recognized as an epidemic some 20 years ago, the NIAID took the lead at the NIH in swiftly mobilizing key stakeholders, planning research, providing resources, and translating basic findings into clinical practice.

The NIAID has already convened a Blue Ribbon Panel of experts to review a strategic plan prepared by NIAID to guide the effort against bioterrorism. Some elements of the plan include establishing Extramural Centers of Excellence for Bioterrorism and Emerging Infections around the country so that scientists can have the tools and the secure facilities they need to conduct their work; continuing the study of the genetics of microbes that might be used in bioterrorism; launching challenge grants to industry and academic centers to attract their long-term interest; and supporting clinical trials of next-generation vaccines and therapeutic agents. The Nation's research enterprise is alert to this urgent need and eager to expand its efforts.

TRANSLATING RESEARCH INTO PRACTICE

Clinical research, or studies involving patients and healthy volunteers, is the crucial step for translating basic science into better health for everyone. Our new age of medical research—capitalizing on the Human Genome Project, the new field of proteomics, and advanced imaging technology—is providing unprecedented opportunities to design new ways to prevent, diagnose, and treat many diseases and

conditions. But we will not realize the promise of new knowledge and new techniques without clinical research—and well-trained clinical researchers—to bring findings from the laboratory to the patient. Our clinical trials have become wider-ranging, more representative of the population, and larger—and they must become even more so in the future. In FY 2003, the NIH will place additional emphasis on clinical research.

For example, the National Institute on Aging (NIA) is accelerating research to slow the progress of Alzheimer's disease, to delay its onset, and to prevent the disease entirely. Already scientists have identified new targets to block directly the effects of the disease in the brain and are developing imaging and other tests to diagnose people in the early stages of the disease. Major prevention trials are under way using vitamin E and the drug Aricept, as well as folate, anti-inflammatory drugs, and estrogen. The NIA is also funding a five-year initiative to speed the development of immune-based approaches and other novel strategies for preventing Alzheimer's disease.

Another example: The National Institute of Neurological Disorders and Stroke (NINDS) will support a network of acute stroke centers across the United States, each capable of treating patients rapidly and serving as a clinical laboratory for scientific studies related to acute stroke, including tests of new drugs. The first effective treatment for acute ischemic stroke, the drug TPA, is only partly effective and cannot be used for all types of strokes. The NINDS has demonstrated the potential of others drugs for stroke in laboratory studies, and translating those findings into practical treatments would be enhanced by state-of-the-art centers for stroke.

The potential of such clinical studies to improve the Nation's health has made even more urgent our need to recruit and retain highly qualified health professionals as clinical investigators. The NIH plans to expand its current Extramural Loan Repayment Program for Clinical Researchers, which provides for repaying the educational loans of qualified health professionals who agree to conduct clinical research. The FY 2003 President's budget request doubles this program by providing $28 million over the FY 2002 estimate.

RESEARCH ON DISEASE PREVENTION

Research to prevent disease has been a major aspect of the NIH's mission, and we plan to launch a number of prevention initiatives in FY 2003, while continuing others started earlier. Although considered a traditional approach, vaccines are effective forms of prevention, and today's vaccine research takes advantage of the most up-to-date knowledge and technology. NIH scientists and NIH-supported scientists are producing and testing vaccines aimed at preventing otitis media (which causes ear infection and sometimes hearing loss in children), Ebola (an often fatal disease caused by a virus found in parts of Africa), dengue fever (a viral disease spread by mosquitoes), HIV/AIDS, Leishmania (a devastating disease spread by sandflies in the subtropics), and malaria. Just last month, scientists at the National Institute of Child Health and

Human Development announced the development of the first vaccine against *Staphylococcus aureus* (often called "staph"), a major cause of infection and death in hospital patients.

Also last month, scientists supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) reported the results of the Diabetes Prevention Program. The research conveys a powerful message of hope to individuals at risk for type 2 diabetes, a life-threatening disease that has been increasing in this country parallel to the increase in obesity. The study showed that millions of overweight Americans at high risk for type 2 diabetes can delay and possibly prevent the disease with improved diet and moderate exercise. The same study found that the oral diabetes drug metformin also reduces the risk of type 2 diabetes, but not as effectively as lifestyle changes.

We know that lifestyle patterns contribute greatly to the risk of developing type 2 diabetes. Thus, the great challenge now is to identify those at risk for type 2 diabetes and encourage them to act on the findings of the study. We are prepared to do that since our legislative authority and the traditional mission at the NIH has always included both disseminating the results of research and communicating general health information directly to health care professionals, patients, and the public. In cooperation with the Centers for Disease Control and Prevention (CDC), the NIH has already launched the National Diabetes Education Program to increase public awareness of diabetes, its risk factors, and strategies for preventing diabetes and its complications.

OTHER FEATURES OF THE BUDGET REQUEST

Mr. Chairman, this is only a brief summary of our emphasis areas now and in FY 2003. Our research portfolio is so broad, deep, and complex that, even in many more pages, I would still not be able to give a complete picture. Yet I am confident that the FY 2003 budget request enables the NIH to sustain momentum of research already in progress, to open the way to new research opportunities in the coming fiscal year and in years to come, and to augment both our research infrastructure and our human capital. In FY 2003 the President's budget request would fund a total of 9,854 new, competing research grants, or a total of 38,038 awards, the highest annual total ever. Intramural research increases by 15 percent over the FY 2002 estimate, with most Institutes and Centers increasing by 9 percent, while the NIAID and the NCI increase by 52 percent and 11 percent respectively, as a result of the large increases in bioterrorism and cancer research. The Research Management and Support (RMS) funds are vital, if the NIH is to manage its programs and resources efficiently and effectively. The RMS funds are used by the NIH to sustain, guide, and monitor extramural and intramural research activities. This funding increases by 17 percent in total in FY 2003. All Institutes and Centers except the NIAID and the NCI increase by 9 percent over the FY 2002 estimate. The NCI and, in particular, the NIAID are requesting increased resources in RMS funding to effectively manage their large program increases.

Mr. Chairman, this concludes my opening statement. I would be glad to respond to any questions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Andrew C. von Eschenbach
National Cancer Institute

on

Fiscal Year 2003 President's Budget Request
for the National Cancer Institute

Mr. Chairman and Members of the Subcommittee:

I am Dr. Andrew von Eschenbach, the Director of the National Cancer Institute (NCI). I am pleased to appear before you to discuss some of the activities supported by the NCI and to present the President's budget proposal for fiscal year 2003. The significant budget increases over the past several years have allowed the NCI to continue on an aggressive path of discovery in cancer research. This path is aimed at the development of interventions that will continue to reduce the suffering and death caused by cancer.

Over the past 30 years, our nation has invested a great deal of its resources in cancer research. It is an investment that has enabled the NCI to conduct research and to support thousands of scientists throughout this country. It is an investment that has sustained promising research and more recently, data-sharing infrastructures and multidisciplinary collaborations. And it is an investment that is now paying significant scientific dividends. Where major breakthroughs were once measured in years or even decades, we are now moving forward at record pace. Every day, we uncover yet another footprint in the genetic and molecular process by which a cell becomes malignant, grows uncontrolled, invades, metastasizes, and ultimately kills.

While our knowledge of this complex process is still rudimentary, the path ahead is now clear and greater dividends are within reach. Even with our just emerging picture of cancer, we are exploiting this knowledge to devise better imaging and diagnostic tools and design new interventions to treat and prevent this devastating disease.

We stand on the threshold of a biomedical revolution, where multidisciplinary collaboration will translate the breakthroughs of basic research swiftly from the lab to the bedside. One recent example of success emerged in the fight against ovarian cancer, one of the deadliest cancers for women, in part due to lack of effective screening methods. A sophisticated computer-based screening tool has shown the ability to recognize protein profiles

in the blood from women with diagnosed ovarian cancer and uses the information to detect new cancer cases in women at an early stage of disease. Current discovery of such molecular signatures of cancer may also make possible powerful, new tools for detecting cancer and its recurrence.

The elucidation of the biology of cancer is a scientific pursuit. But the eradication of cancer is a human experience. The ultimate goal of the people of the National Cancer Institute is saving lives and improving the quality of life among cancer patients.

CANCER TRENDS

Five years ago, NCI initiated an annual report to the Nation on the burden of cancer. This report is developed in collaboration with the American Cancer Society (ACS), the North American Association of Central Cancer Registries, the Centers for Disease Control and Prevention and its National Center for Health Statistics. Based on statistics from these sources, we are continuing to see encouraging overall trends, including continued decline in the rate of new cancer cases and cancer deaths.

Today, we can successfully treat or increase life expectancy for more than half of all cancer patients. We now have more options for prevention, including chemoprevention such as tamoxifen for breast cancer, and are developing more evidence-based interventions for cancer control. Adult smoking is down dramatically from the 1960s for men and the increase in smoking among women has finally reached a plateau. The latest statistics from the Report to the Nation that we will release this spring also show that while breast cancer incidence continues to rise (due to increase in early stage disease), overall breast cancer deaths continue to decline. And for the first time ever, we are seeing a small, but significant decline in breast cancer mortality among African-American women.

Yet even as these trends give rise to hope, they must also steel our resolve to use the fruits of discovery to the further benefit of patients. That's because we know that this year, based on ACS estimates, over 1.2 million Americans will be diagnosed with cancer this year, and about 550,000 Americans are expected to this disease, more than 1,500 people a day. The number of new cancer cases is still rising for some cancers such as esophageal, liver, melanoma, and non-Hodgkin's lymphoma. And there remains a disparate burden of cancer experienced by America's undeserved population. Another trend indicates that youth smoking continues to rise except in states with vigorous tobacco control programs. NIH estimated the overall costs for cancer to be $156.7 billion in the year 2001.

Of course, behind these numbers lies the real and human face of cancer. It is the face of a child with retinoblastoma whose only hope is radical surgery that will leave him cured but permanently blind. It is the face of a young woman living with the fear that her breast cancer will recur. And it is the face of a grandfather whose lung cancer has shattered his dream of spending his golden years with his grandchildren.

These faces demand urgency. It is an urgency that will be at the forefront of NCI's continued efforts to translate research quickly and safely to the cancer patient. I have highlighted several activities that illustrate NCI's accelerated approach to scientific discovery.

HIGHLIGHTS IN CANCER RESEARCH

We understand that improved technology for early detection and diagnosis is critically needed for cancer to become a rare disease. For this reason, imaging research supported by NCI is advancing on several fronts. Now, with the recent reawakening of debate on mammography guidelines, it is more important than ever to redouble our efforts in this area. In addition to assuring women that the weight of the evidence still shows that mammography saves lives, NCI is accelerating research into better screening tools. Besides efforts to improve conventional and digital X-ray mammography, NCI supports research for several other technologies such as magnetic resonance imaging (MRI), ultrasonography, positron emission tomography (PET), and single photon emission computed tomography (SPECT). Already, with these technologies, scientists can "see" biological processes taking place in living tissues such as blood flow, oxygen consumption, and glucose metabolism.

A major research effort is also under way to create molecular imaging technologies that can noninvasively detect and display the actual molecular events taking place in the body. Imaging technology to detect cancer recurrence using flurodeoxyglucose (FDG) PET scans and dynamic MRI for functional therapy monitoring are among the sophisticated imaging techniques currently being investigated.

In addition, several PET studies are in progress for the evaluation, staging and monitoring of therapy using PET for woman with breast cancer. In a large clinical trial from the University of Pennsylvania, doctors are incorporating dedicated breast PET into the standard diagnostic regimen for women with breast cancer.

On the therapeutic front, researchers are making headway against certain forms of leukemia, where an abnormal protein complex called bcr-abl forms inside the cell and stimulates uncontrolled growth. A search for agents that would interfere with bcr-abl led to the identification of STI-571, later renamed imatinib mesylate (Gleevec®). In clinical trials with this drug, more than 50 percent of patients with myeloid blast crisis responded well as measured by a decrease in the abnormal leukemic blood cells. Gleevec® has moved swiftly from clinical trials to the cancer centers and is now available as treatment for patients with chronic myelogenous leukemia (CML). This drug is now being evaluated in the treatment of ovarian, certain types of brain cancer, as well as a very rare form of stomach cancer and prostate cancer.

In the area of prevention, research is pointing to certain agents that are capable to changing a person's risk for cancer. When basic research establishes a biological basis for an

intervention, trials serve to test the hypothesis. For example, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) will determine if seven or more years of daily supplements of selenium and/or vitamin E reduces the number of new prostate cancers diagnosed in healthy men. In addition, a Study of Tamoxifen and Raloxifene (STAR) will determine whether the osteoporosis drug raloxifene has equivalent breast cancer risk reduction benefits with reduced risk of side effects as compared to tamoxifen.

While the fast pace of discovery from these and other areas is welcome, the volume of data generated can often be overwelming to the research community. To address this, NCI supports a fully integrated cancer biology approach to discovery through a discipline called bioinformatics. NCI programs such as the Cancer Genome Anatomy Project (CGAP), the Proteomics Initiative, Mouse Models Program, the Drug Discovery Program produce information and enable the research community nationwide to access these Web-based data sets that serve as tools for collaboration and scholarly discovery. This ensures that the analyses and interpretation of data across disciplines proceed in parallel and synergistically so that discovery in one system informs research in the other.

Bioinformatics enables researchers in CGAP to build, analyze, and interpret databases of genes expressed in cancer cells and of single nucleotide polymorphisms (SNPs), important markers for cancer risk-related genes. In proteomics, the ovarian detection tool that I mentioned earlier has demonstrated the power of bioinformatics to detect invisible patterns of disease. And in drug discovery, bioinformatics ensures that the most promising targets identified in the extramural research community can be exploited using the modern tools of cell-based drug analysis and gene-based high-throughput screening.

MAINTAINING MOMENTUM

Much of the research I've highlighted is being conceived and conducted by scientists in laboratories and clinics across the country and at NCI – building on the wellspring of scientific discovery. Our goal for Fiscal Year 2003 is to speed the rate of discovery and translation of those discoveries to cancer patients by expanding and facilitating researchers' access to resources and new technologies. To understand the basic processes of cancer and translate this research into clinical practice, we must link researchers with the resources and technologies they need while encouraging multi-disciplinary collaboration.

NCI will continue to create and sustain research infrastructures for collaboration, technology support and development, and access to resources that enable multiple scientific disciplines to address the complex questions before us. We will achieve this by expanding our nationwide infrastructure of cancer centers, centers of research excellence, networks, and consortia in ways that promote and facilitate complex scientific interactions and the sharing of information and resources.

Two important programs deserving of special mention are Rapid Access to

Intervention Development (RAID) and Rapid Access to Preventive Intervention Development (RAPID). These programs expedite new agent development on the part of independent investigators in universities or biotechnology companies by making NCI's preclinical drug development resources and expertise available for moving novel molecules toward clinical trials.

Also key to our multidisciplinary approach are Specialized Programs of Research Excellence (SPOREs). Several major academic centers of excellence are now working on a wide range of scientific approaches to translational research – that is, focusing on the biology of cancer specifically as it may inform development of new treatments. NCI will expand the use of SPOREs in the coming year.

We will continue our efforts to ensure that the clinical trials program addresses the most important medical and scientific questions in cancer treatment and prevention quickly and effectively through state-of-the-art clinical trials that are broadly accessible to cancer patients, populations at risk for cancer, and the physicians who care for them. Despite major advances in our understanding of tumor biology and potential molecular targets for cancer prevention and treatment, our capacity to apply and test these findings in clinical settings has not kept pace. The NCI will invest more resources in developing and testing new therapies and increasing access to and participation in clinical trials.

We will also expand surveillance data systems, methods, communications, and training to improve capacity for monitoring progress in cancer control and for exploring potential causes of cancer nationally and among diverse, underserved populations.

NCI is also launching research to improve the quality of cancer care by strengthening the information base for cancer care decision making. Researchers must better understand what constitutes *quality* cancer care, with an emphasis on the patient's perspective; identify geographic, racial/ ethnic, and other disparities in who receives quality care; and strengthen the scientific basis for selecting appropriate interventions.

Finally, to sustain new ideas, we will continue to nurture and develop new scientists. To deliver new biology-based interventions, we must educate and train capable physicians. That's why NCI will continue to expand its efforts to design and implement opportunities for scientists at all career levels to meet the challenge of building a stable, diverse cadre of basic, clinical, behavioral, and population scientists trained to work together effectively and use the most advanced technologies.

CLOSING

NCI's mission is broad and our approach is necessarily ambitious, because, while our primary role and our expertise is research, our focus and sense of urgency is in serving the American people, the country's cancer patients and their families, friends and neighbors.

As director of NCI, a doctor, an investigator, and a cancer survivor, I share the urgency of America's cancer patients and I am confident that the efforts I've highlighted and many additional activities will bring us closer to the ending the death and suffering caused by this disease.

BUDGET STATEMENT/GPRA

I am pleased to present the President's budget request for the National Cancer Institute for FY 2003, a sum of $4,724,505,000, which reflects an increase of $514,784,000 over the comparable Fiscal Year 2002 appropriation.

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compares to our FY 2001 results to the goals in our FY 2001 performance plan.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Claude Lenfant
Director, National Heart, Lung, and Blood Institute

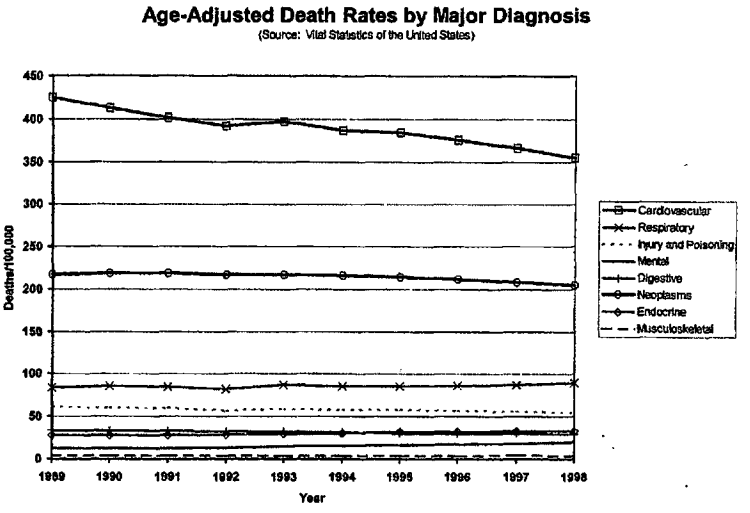
on
Fiscal Year 2003 President's Budget Request
for the National Heart, Lung, and Blood Institute

Mr. Chairman and Members of the Committee:

I am pleased to address this Committee once again on behalf of the National Heart, Lung, and Blood Institute (NHLBI) and, in particular, to thank the Committee for its longstanding and generous support of the Institute's research programs. Let me begin by commenting on where we stand with regard to diseases of importance to the NHLBI, and then move on to describe several promising new research directions.

BURDEN OF DISEASE

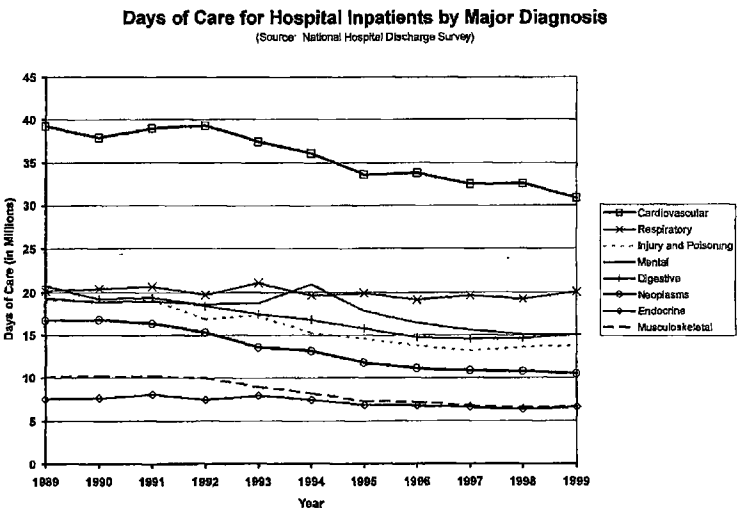
The first chart below, which summarizes mortality during the most recent 10 years for which data are available, provides welcome reassurance that the decline in the death rate for cardiovascular diseases is continuing the trend that began several decades ago. I believe it is fair to say that medical science has made more progress in this area than in any of the other major disease categories. This reflects the wisdom of our great investment in research, which has yielded unprecedented advances in treatment, both medical and surgical, and widespread attention by the public and the medical establishment to addressing risk factors such as hypertension and blood cholesterol.



Nonetheless, it is equally and starkly apparent that we in this country are far more likely to die of cardiovascular diseases than of any other cause.

Of equal or perhaps more significance is the societal burden of *living* with disease. One measure of this burden is time spent in the hospital. As the chart on the next page indicates, cardiovascular disease patients spend more than 30 million days per year in acute-care hospitals, and respiratory ailments are the second most common reason for hospitalization. Beyond the pain and suffering, the cost associated with these hospitalizations demands our attention.

The enormous cost of treating diseases of concern to the NHLBI was also made apparent in a study published in the January 16, 2002, issue of the *Journal of the American Medical Association*. Reporting the results of a nationwide survey, the researchers identified medications that are most commonly taken. Fourteen of the top 21 prescription drugs address cardiovascular, lung, or blood problems. And, these data most assuredly understate the cost of treatment, given that many such drugs (e.g., beta blockers, statins) are underprescribed, and patients with limited financial resources are



generally inclined to spend their money on medications that make them feel better (e.g., for menopausal symptoms, hay fever, arthritis pain, or depression) before they spend money on drugs to treat conditions such as hypertension and high cholesterol that, however threatening, produce no symptoms.

BASIC RESEARCH

As always, basic research is one cornerstone of our effort to alleviate the burden of disease. In this arena, we have been able to capitalize on our budget increases by putting into place a number of activities that would have been impossible under other circumstances. An example is our Programs in Genomic Applications, which seek to maximize the fruits of the new information about the human genome in order to identify the causes of disease, determine who is susceptible to it, and tailor treatments and, possibly, cures to the individual.

We are moving forward on other basic science fronts, based on recent scientific findings. For instance, we are stimulating research on cell-based therapy in the wake of astonishing discoveries that, contrary to everything we thought we knew before, cells of the heart and other organs are capable of regeneration. Examining hearts of people who had suffered fatal heart attacks, researchers found dividing cells in the area of the damaged heart muscle. Furthermore, doctors studying male patients who received heart transplants from female donors found evidence that male cells had somehow arisen and

incorporated themselves into the donated heart tissue. If we could find a way to harness and direct the body's ability to regenerate cells, we would have an entirely new approach to therapy for diseases that are currently irreversible, such as heart failure.

Accumulating evidence suggests that inflammation – the body's normal, protective response to injury or infection – may be at the core of many chronic degenerative diseases. Its role in asthma has been well established, and reports that blood levels of a substance called C-reactive protein, a marker of inflammatory activity, are correlated with risk of heart attack and stroke suggest a role in atherosclerosis as well. Understanding the delicate balancing act of the immune system could pave the way for new preventive and therapeutic strategies. Related work from a number of laboratories has found that exposure to a variety of infectious agents, both viral and bacterial, is associated with development of vascular disease and of chronic obstructive pulmonary disease. We are vigorously pursuing basic research to elucidate the mechanisms underlying these phenomena in the expectation that it may ultimately lead to new approaches, perhaps even vaccines, to prevent disease.

The quest to develop gene therapies made a significant step forward this year. Researchers used HIV – the AIDS-causing virus that is notorious for its ability to find its way into the nuclei of cells – to deliver a therapeutic gene to the bone marrow of mice with sickle cell disease. A cure resulted. Before such a therapy can be attempted in human patients, more basic research is needed to establish its safety and develop a non-toxic way to rid the body of sickled cells – goals that we are supporting strongly.

CLINICAL RESEARCH

As we pursue these and other basic research avenues, we are working to strengthen clinical research to ensure that findings from the laboratory have a swift and effective impact on patient care. Our research centers program is being reconfigured as Specialized Centers of Clinically Oriented Research (SCCORs) to sharpen its focus on the patient. We have made competitive funds available for investigators involved in SCCORs, clinical networks, and multicenter clinical trials to develop skills-development programs to enhance the training and career development of clinical investigators. We have made known to the community our strong interest in supporting Mentored Patient-Oriented Research Career Development Awards and Midcareer Investigator Awards in Patient-Oriented Research. And, we have worked with other NIH components to craft loan repayment programs that will encourage clinically trained individuals to funnel their talents into research.

EDUCATION AND OUTREACH

To maximize the impact of research findings on the people whom we serve, the NHLBI is strongly committed to educating patients, health professionals, and the public about disease awareness, diagnosis, treatment, and prevention. The National Asthma Education and Prevention Program (NAEPP), for example, has developed and disseminated guidelines for asthma diagnosis and management; produced practical guides for patients, emergency department personnel, pharmacists, nurses, and schools; conducted media campaigns to promote asthma awareness among the general public and to encourage undiagnosed patients to seek care; and worked with communities to develop coalitions to address local asthma issues. The NAEPP serves as a focal point for coordination of all federal activities related to asthma, and has developed a plan to enhance collaboration among relevant agencies. And, finally, the impact of the NAEPP is being felt worldwide through the Global Initiative on Asthma, conducted in partnership with the World Health Organization.

AMOUNT OF PRESIDENT'S REQUEST

I am pleased to present the President's budget request for the NHLBI for FY 2003, a sum of $2,798,178,000, which reflects an increase of $216,618,000 over the comparable Fiscal Year 2002 current estimate.

GOVERNMENT PERFORMANCE AND RESULTS ACT

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's third annual performance report which compared our FY 2001 results to the goals in our FY 2001 performance plan.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Lawrence A. Tabak
National Institute of Dental and Craniofacial Research

on

Fiscal Year 2003 President's Budget Request
for the National Institute of Dental and Craniofacial Research

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 FY 2003, a sum of $374,319,000, which reflects an increase of $29,016,000 million over the comparable Fiscal Year 2002 appropriation. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report, which compared our FY 2001 results to the goals in our FY 2001 performance plan.

IMPROVING THE NATION'S ORAL HEALTH

Over the past 50 years, our nation's investment in dental, oral, and craniofacial research has yielded tremendous advances in American public health. At this time when our nation is engaged in a war, it is interesting to reflect back to the World War II era when many patriotic, able-bodied young men were rejected from military service because they lacked the mandatory six opposing teeth to enlist in the military. In hopes of countering this public health problem, Congress established in 1948 the then National Institute of Dental Research to help eradicate dental decay and tooth loss in America.[1] Today, NIDCR and its partners in public health reflect with pride upon the fact that few young men and women lose teeth. In addition, 70 percent of older Americans have not lost their teeth, compared to 54 percent just 20 years ago.[2]

COMMITMENT TO REDUCING HEALTH DISPARITIES

The NIDCR's mission to improve the nation's oral health remains far from finished, however. One reason is the sobering fact that many of the nation's oral health advances have yet to adequately benefit our underserved populations. Specifically, there is a clear and compelling need to push forward and reduce the higher incidence of oral cancer, gum disease, and tooth decay among the underprivileged in our society. The NIDCR remains firmly committed to forwarding this effort and pursuing it to its rightful conclusion. As a first step, NIDCR, in collaboration with the National Center for Minority Health and Health Disparities, has funded five Centers for Research to

Reduce Oral Health Disparities in Boston, New York, San Francisco, Seattle, and Detroit. Another large study has been funded to examine the underlying causes of oral health disparities in rural West Virginia. This multi-year investigation will focus on the unusually high incidence of children born in this region with cleft lip and palate. The hope is that, with inexpensive dietary interventions during pregnancy, more mothers will give birth to babies free of this socially stigmatizing, expensive-to-treat problem.

UNPRECEDENTED OPPORTUNITY FOR SCIENTIFIC DISCOVERY

The NIDCR leadership also recognizes that scientists today truly stand on the threshold of an unprecedented "Golden Age" in biology. The recent completion of the Human Genome Project, in tandem with the emergence of more powerful research technologies in the laboratory, are allowing scientists to catalogue with encyclopedic comprehensiveness the actual genes, proteins, and protein networks that power our cells. Such studies, an impossibility just a few years ago, have opened a valuable window into the genetic programs of some of the most complex developmental and disease processes involving oral and craniofacial tissues.

TMJ DISORDERS: BUILDING THE SCIENTIFIC INFRASTRUCTURE

Given the tremendous opportunity that now exists for fundamental discovery in biomedicine, NIDCR has targeted as one of its high-priority research areas for FY 2003 a group of conditions collectively known as temporomandibular joint (TMJ) disorders. These disorders affect the joint that connects the lower jaw (mandible) to the skull and the surrounding muscles that are used to chew and open the mouth. An estimated 5 to 12 percent of Americans report having pain associated with the temporomandibular joint. Studies suggest that TMJ disorders may be as much as two times more common in women than men.

By investing in this new initiative, the Institute plans to create the needed research infrastructure to allow multi-disciplinary teams of scientists to more rapidly and systematically tease out the molecular and physiological basis of these conditions. Only then can rational and targeted treatment approaches be devised to help control or alleviate the chronic pain and dysfunction that people with these conditions confront on a daily basis.

To begin building the needed research infrastructure, NIDCR plans to establish the first registry for people with TMJ disorders. The registry will help track the incidence and natural history of these conditions, a longstanding need in the field. The NIDCR also will make a concerted effort to identify biomarkers -- genes, proteins, or even protein networks -- that are adversely affected by TMJ disorders. Through this research, the Institute hopes to lay the intellectual foundation for the development of

tests that generate meaningful, telltale diagnostic or prognostic information for doctors and patients. The Institute also will invest in the development of animal models that closely mimic TMJ conditions, providing an important scientific tool to test emerging hypotheses as the research progresses.

RELIEVING ACUTE AND CHRONIC PAIN

One of the great challenges today in medicine is the management of pain. Yet, because most people experience pain differently, its study can be a lot like trying to analyze multiple moving targets at once. Among the variables involved in the pain process are: age, immune function, endocrine and neural activity, genetics, stress, psychological state, gender, and even cultural background.

Despite the inherent complexity of their work, NIDCR scientists and grantees continue to make progress in understanding the dynamics of pain and how to effectively control it in dental care and for pain sufferers in general. Recently, for example, NIDCR researchers used positron emission tomography (PET) to image the brain's chemical activity while human volunteers received a stimulus mimicking the chronic pain of temporomandibular joint disorders. This marked the first time ever that scientists had non-invasively analyzed sustained pain, while also (1) simultaneously monitoring brain scans of a key neurochemical system and (2) recording the self-reported pain ratings of human participants.

The NIDCR scientists found that after experiencing pain in the jaw muscles for 20 minutes, the volunteers had a surge in the release of natural opioids, part of the brain's painkilling system, and a concomitant drop in pain and pain-related emotions. But, most significantly, the researchers discovered a major variation among volunteers in the baseline and pain-induced levels of naturally occurring opioids. Interestingly, when comparing placebo and pain-inducing conditions, the activation of the anti-pain response was dramatic in some volunteers, while in others it was much less pronounced. Those who had the greatest change tended to report the lowest experience of pain, both in its sensory and emotional aspects.

This study provides new insights into the importance of the body's natural painkiller system and the reasons why each of us experiences pain differently. The results also show how brain chemistry regulates sensory and emotional experiences. The findings may help researchers better understand prolonged pain and find more effective ways to relieve it.

LEARNING TO REGENERATE ORAL AND CRANIOFACIAL TISSUES

The physical complexity of the human head and face has captured the imagination of artists since the beginning of time. However, this exquisite complexity

sometimes can be problematic for clinicians who must treat injuries, diseases, and genetic defects of the craniofacial region. A noted example is the relatively rare genetic disorder, ectodermal dysplasia (ED). Children born with ED often have malformed and missing teeth, meaning they must cope with the rigors of wearing dentures for a lifetime. Yet, if scientists could learn to trick the body into regrowing a full set of healthy teeth, the quality of life for these children would be greatly enhanced. The NIDCR leadership believes that the opportunity now exists to discover in a more rational, systematic manner how to effectively manipulate the body's developmental signals to regenerate oral and craniofacial tissues. To help forward this potentially high-yield research, the NIDCR plans to launch an initiative to develop biomimetic, tissue engineering, and stem cell approaches to restore craniofacial tissues. Specifically, the initiative will focus on learning how to repair and regenerate teeth, gums, and the bones that support these tissues; learning how to restore salivary gland function to help people with Sjögren's syndrome; and learning to develop diagnostic and treatment strategies for temporomandibular joint repair and restoration.

REDUCING THE BURDEN OF ORAL CANCER

Most Americans have heard that early detection is often critical to beat cancer. Though this principle has been difficult to apply to some hard-to-access areas of the body, such as the pancreas and the ovaries, that is not the case for many oral cancers. Precancerous oral lesions are often visible to the eye and readily accessible for biopsy.

Yet, according to American Cancer Society estimates, 7,400 Americans will die this year--in most cases needlessly--from oral and pharyngeal cancer. That totals an estimated 74,000 Americans who will succumb to oral cancer during the decade. Thousands more will undergo multiple surgeries to remove advanced tumors and reconstruct their faces and oral cavities.

What can be done to improve this needless public health problem? The NIDCR has invested in several approaches, starting with efforts to heighten public and professional awareness of oral cancers. NIDCR has funded an initiative to assess the rate of oral cancer in five states - New York, North Carolina, Florida, Michigan, and Illinois. At the same time, this initiative will assess public and professional knowledge of oral cancer risk factors, while also documenting and evaluating the practices used to diagnose oral cancers among various health professions. Included in this research is an assessment of the important public health question: How likely is it that an American will receive an annual oral cancer examination from a healthcare provider? The data generated from this research will allow individual states to tailor intervention strategies to their specific demographic and professional needs. Already, based on the results of an earlier pilot project, Maryland has developed a targeted training program for its

health professionals on how to examine patients for oral cancer and identify early, developing lesions.

Secondly, NIDCR has invested in research to develop powerful new tests for the rapid diagnosis of oral cancer. The latter is an important point because, as with all cancer sites, abnormal lesions in the oral tissues can be difficult to characterize by simply staining and looking at them under a microscope. In fact, using current diagnostic tests, it is impossible to know whether a suspicious oral lesion indeed will turn cancerous. Neither is it possible to determine whether a cancer will grow rapidly or slowly. Since current diagnostic tests cannot read the so-called "molecular signatures" of biopsied tissue--information that would greatly increase diagnostic specificity.

With the arrival of more powerful laboratory tools over the past decade, NIDCR scientists and grantees have helped to identify many molecular glitches that trigger oral cancer. In fact, the step-by-step progression model for oral cancer is among the most well developed in all of oncology. Given the tremendous potential for progress in the study of these deadly cancers, NIDCR has invested in powerful new molecular technologies that could yield improved diagnostic tests for oral cancers. Already, work is under way to develop a small computer chip--about the size of a quarter--that contains hundreds of genes associated with oral tumors and their metastasis. This chip, if validated, could offer a genetic sensor as an early warning system for a developing oral cancer.

Work also is under way to design a related diagnostic chip that doctors one day could use to detect, in a matter of minutes, the abnormal activity of the very proteins that trigger oral cancers. Such a level of molecular and diagnostic specificity has been a longstanding goal of science, and the great promise of molecular medicine is now closer at hand than ever.

With its longstanding commitment to scientific excellence, NIDCR will continue in coming years to support basic and clinical advances to improve the nation's oral health. This investment in the power of research represents not only hope for millions of Americans today, but improved health and quality of life for generations to come.

STATISTICAL REFERENCES

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Allen M. Spiegel
National Institute of Diabetes and Digestive and Kidney Diseases

on

Fiscal Year 2003 President's Budget Request
for National Institute of Diabetes and Digestive and Kidney Diseases

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 FY 2003, a sum of $1,609,292,000, which reflects an increase of $138,477,000 over the comparable Fiscal Year 2002 appropriation. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report, which compared our FY 2001 results to the goals in our FY 2001 performance plan. I appreciate the opportunity to testify on behalf of the NIDDK, which supports research on a wide range of chronic, debilitating diseases. My testimony will highlight some examples of research progress, opportunities and plans.

DIABETES

In type 1 diabetes, immune system destruction of insulin-producing beta cells leads to lifelong dependence on insulin injections for survival. Last year, I told you that a team of researchers from Edmonton, Canada, had restored natural insulin production in a small number of patients by transplanting clusters of insulin-producing beta cells, called islets, taken from donor cadaver pancreases. This year, I am very pleased to report that scientists in a recently-established NIDDK intramural Transplantation and Autoimmunity Branch have achieved similar positive results in several patients. While we must closely monitor these patients to weigh the long-term effects of therapy, these early results are very encouraging. They provide an important "proof of principle" that islet transplantation can develop into a viable treatment for type 1 diabetes. The current shortage of cadaver pancreases, however, poses a beta-cell supply problem that must be solved if islet transplantation is to become a widely available treatment option. To address this problem, we have launched a multifaceted initiative to learn all we can about insulin-producing cells through a revolutionary "Comprehensive Beta Cell Project." This project will reveal the intricacies of beta cell biology, and define the patterns of gene expression at every stage of beta cell development within the pancreas. These studies will help researchers find ways to generate an unlimited supply of new beta cells for transplantation therapy in type 1 diabetes. Moreover, they should help

clarify the basis for the failure of beta cells to secrete adequate amounts of insulin in type 2 diabetes. As we strive to develop a cure for type 1 diabetes, we are also working diligently to prevent new cases in those at risk. Building on expanded knowledge of the immune system, we have launched a nimble clinical TrialNet to ensure rapid pilot testing of innovative ways to prevent disease onset. In this way, the most promising approaches can be readily propelled into larger multi-center clinical trials.

In parallel with our beta cell efforts, we are pursuing stem cell biology--not only as a source of islets for cell-based therapy of type 1 diabetes, but also for its application to a host of other diseases, such as end stage liver disease, in which transplantation is curative, but inadequate organ supply limits the number of patients who can receive transplants. Our initiatives are consonant with extensive previous work on bone-marrow-derived and other adult stem cells, and with the President's decision to permit NIH funding of research using certain existing human embryonic stem-cell lines. With advice from an external strategic planning group, we have developed a linked series of initiatives and planned genomics projects to capitalize on the enormous promise that stem cells hold for restoring tissues and organs ravaged by disease. These initiatives will explore the versatility of progenitor stem cells to differentiate into virtually any specific cell type in the body.

In type 2 diabetes, we are tackling a public health problem of epidemic proportions, fueled by the rising tide of obesity in the U.S. The prevalence of diabetes in adults is eight percent, equating to about 16 million people.[1] The number of Americans who have diabetes has increased 49 percent from 1990 to 2000 and is expected to burgeon further in the decade ahead.[2] Compounding today's grim statistics are particularly troublesome reports that both type 2 diabetes and obesity are on the rise in children and teens. This trend is especially strong among minority groups, such as Native Americans, Mexican Americans and African Americans, in whom adults are already disproportionately affected by both conditions. Thus, today's epidemic may well be the tip of an iceberg that will surface--with great menace for our health care system--as these newly affected youngsters grow into adulthood.

Prevention is a critical means of halting the dual burden of diabetes and obesity. While treatments exist for those already affected, no strategy can be better than preventing, from the very outset, the interlinked health problems of type 2 diabetes and obesity. Impressive proof that prevention really works comes from our major clinical trial in type 2 diabetes, the Diabetes Prevention Program or DPP. Last year, I testified that we were nearing this trial's completion--hopeful of positive results. Today, I can report that the final results have far surpassed our hopes. So strikingly positive are the findings that we ended the trial one year ahead of schedule. The results were announced by Secretary Thompson at a press conference held at NIH on August 8, 2001, and reported in detail in The New England Journal of Medicine on February 7, 2002. With a lifestyle intervention consisting of only modest changes in diet and exercise, the development of type 2 diabetes was reduced by 58 percent in individuals at high risk for developing the disease. The beneficial effect of the lifestyle intervention

applied across all racial, ethnic and age groups. Minority groups comprised 45 percent of the study population, and 20 percent were 60 years of age or older--thus demonstrating that this prevention strategy can be realistically applied to the diverse U.S. population. In another arm of the study, the diabetes medication metformin was also effective, reducing the development of diabetes by 31 percent, but the drug was effective only in younger and heavier individuals. Now, armed with the impressive results of the DPP, we must translate these successful prevention approaches to the 20 million Americans with impaired glucose tolerance who are at high risk for the disease --with emphasis on the 10 million at greatest risk. To this end, we are launching an initiative to develop cost-effective methods to identify those at high risk and to implement the lifestyle intervention on a wider scale. We are also supporting a network of centers to develop effective prevention strategies specifically targeting children at high risk for type 2 diabetes. At the same time, vigorous fundamental research provides a framework for combating obesity by providing insights into the processes regulating appetite and metabolism. Research on fat-cell hormones, such as the appetite-inhibiting hormone leptin, is proving that fat tissue is not a passive depot of energy, but an active participant in regulating metabolic processes. These findings may pave the way to the development of effective drugs to aid weight loss and prevent or reduce obesity. In addition, we will continue to support behavioral research and outcomes research with implications for public health policy--for example, the recent finding that breast feeding may help a mother prevent her child from becoming obese.

For diabetes patients, the major killer is heart disease. Our National Diabetes Education Program has therefore launched a new campaign urging Americans to know their "ABCs." The "A" stands for the hemoglobin "A" 1c test--an integrated measure of blood glucose levels. The "B" for blood pressure and the "C" for cholesterol levels emphasize important prevention strategies that are built on extensive research by the National Heart, Lung and Blood Institute. This "ABCs" program is designed to help reduce mortality from heart disease and stroke in patients with diabetes.

DIGESTIVE DISEASES

In digestive diseases research, I am pleased to announce the identification of the first gene that increases susceptibility to Crohn's disease, a debilitating form of inflammatory bowel disease or IBD. A new IBD Genetics Consortium will take full advantage of this discovery, and also speed the search for other culprit genes in this complex disease. Identification of novel susceptibility genes for Crohn's disease and ulcerative colitis should lead to improved diagnosis and treatments. We are convening a meeting on therapeutic endpoints for clinical trials in IBD to facilitate efficient testing of innovative therapies. We are also augmenting our clinical research efforts in liver disease with a planned consensus conference for hepatitis C treatment, a cohort study of adult-to-adult liver transplantation, and two clinical trial networks–one for nonalcoholic steatohepatitis, a liver disease associated with insulin resistance and diabetes, and a second for biliary atresia, a serious pediatric disorder. We are developing plans for a

hepatotoxicity network to apply advanced genomic methods to the serious problem of drug-induced liver injury.

KIDNEY, UROLOGIC AND BLOOD DISEASES

The incidence of end stage renal disease (ESRD) is increasing at an alarming rate with 300,000 patients currently on chronic dialysis and projections of 600,000 patients on dialysis by 2010.[3] Only 31 percent of dialysis patients survive five years.[4] We are taking multiple steps to address this problem. In addition to emphasizing primary prevention and effective treatment of diabetes--the cause of ESRD in 45 percent of patients--we are establishing a new National Kidney Disease Education Program (NKDEP), which will initially target high risk groups. The NKDEP will promote early recognition of chronic kidney disease, and implementation of treatment measures proven to slow progression to ESRD. For example, our major clinical trial, the African American Study of Kidney Disease (AASK), showed conclusively that treatment with angiotensin converting enzyme (ACE) inhibitors is more effective than calcium channel blockers in preventing hypertensive kidney disease from progressing to ESRD in high-risk African Americans. We are also launching treatment trials for other important causes of ESRD such as polycystic kidney disease and focal segmental glomerulosclerosis. Mortality of patients with chronic renal insufficiency, primarily from heart disease, is extremely high. A new cohort study of patients with chronic renal insufficiency will help shed light on the causes of the cardiovascular mortality that affects these patients, and a trial that lowers homocysteine levels in the blood of kidney transplant patients will test whether this amino acid is responsible for increased heart disease in ESRD patients.

Our portfolio of urology research continues to flourish. This research is uncovering important knowledge about how bacteria attach to the bladder surface, and how we can use these insights to combat antibiotic resistance in the treatment of urinary tract infections. Major clinical initiatives in bladder disorders include clinical research networks to speed the testing of therapies for urinary incontinence and interstitial cystitis. Scientific recommendations of an expert panel, the Bladder Research Progress Review Group, will help guide our program development. Results of our major multi-center trial on Medical Therapy of Prostatic Symptoms (MTOPS) are to be announced later this year. We intend to bolster prostate research by making available biopsy tissue obtained in MTOPS for study by a network of investigators. We will also be launching a trial of saw palmetto and other phytotherapies widely used for symptoms of prostate enlargement.

In blood diseases, our strong portfolio in areas such as hematopoietic stem cell research and globin gene regulation is the basis for clinical advances. We are supporting studies on drugs to eliminate the toxic iron overload that is a byproduct of current treatment for Cooley's anemia. We are also supporting development of new non-invasive methods for accurate measurement of iron burdens in patients.

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

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[4] U.S. Renal Data System.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Audrey S. Penn, Acting Director
National Institute of Neurological Disorders and Stroke

on

Fiscal Year 2003 President's Budget Request
for the National Institute of Neurological Disorders and Stroke

Mr. Chairman and Members of the Committee:

I am Audrey Penn, Acting Director of the National Institute of Neurological Disorders and Stroke. I am pleased to present the President's budget request for NINDS for FY2003, a sum of $1,443,392,000, which reflects an increase of $111,744,000 over the comparable Fiscal Year 2002 appropriation. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compared our FY2001 results to the goals in our FY2001 performance plan.

The mission of NINDS is to reduce the burden of neurological disease–a burden borne by every age group, by every segment of society, by people all over the world. The Institute carries out this mission through research on the healthy and diseased brain, spinal cord, and nerves of the body, which together make up our nervous system. The intricacy of the brain is awesome, its workings are elusive, and an extraordinary variety of disorders affect the nervous system. Furthermore, the brain and spinal cord are difficult to access, sensitive to intervention, and reluctant to regenerate following damage. For these reasons, neurological disorders often defy the best efforts of medicine, even in the modern era.

The last decade has brought the first treatments for acute stroke and spinal cord injury, new immune therapies that slow the progression of multiple sclerosis, and increased drug and surgical options for treating Parkinson's disease, epilepsy, and chronic pain. Continuing advances in preventing stroke and birth defects, such as spina bifida, are also improving the public health. Still, treatments for most neurological disorders are far from adequate, often failing to stop or even slow the disease process. What is encouraging, however, is the variety of new treatment and prevention strategies under development: drugs that home in on the molecules that cause disease, stem cell

therapies that replace lost nerve cells, neural prostheses that read control signals directly from the brain, vaccines that target neurodegeneration, implantable electronic stimulators that compensate for brain circuits unbalanced by disease, and behavioral interventions that encourage the brain's latent capacity to repair itself.

THE BURDEN OF NEUROLOGICAL DISORDERS

Our strategies are shaped not only by scientific insights but also by the sheer variety of neurological disorders. The causes of neurological disorders include trauma, infections, toxic exposure, developmental defects, degenerative diseases, tumors, gene mutations, systemic illness, vascular events, nutritional deficiencies, immune reactions, and adverse effects of essential treatments, such as cancer chemotherapy. Stroke, chronic pain conditions, dementia, and traumatic brain injury are among the leading causes of death and disability in the nation. Epilepsy, spinal cord injuries, multiple sclerosis, Parkinson's disease, the muscular dystrophies, autism, cerebral palsy, and peripheral nerve disorders, are common enough to be familiar to most Americans. But there are many other neurological disorders unfamiliar to most people until a family member is affected, and Congress has been active in bringing attention to less familiar diseases, including amyotrophic lateral sclerosis (Lou Gehrig's disease), Batten disease, the dystonias, facioscapulohumeral and congenital muscular dystrophies, Friedreich's ataxia, mitochondrial disorders, mucolipidosis type 4, neurofibromatosis, reflex sympathetic dystrophy, spinal muscular atrophy, spina bifida, and tuberous sclerosis. A complete list of neurological disorders would include hundreds more.

DIFFERENT DISEASES, COMMON THEMES

As scientists unravel the complex processes that underlie neurological disorders, ranging from acute stroke to the inexorable chronicity of Parkinson's disease, common themes are emerging, leading to the hope that similar therapeutic and preventive strategies will also apply. To put it another way, progress against a single disease is likely to have a bearing on many others. A few examples of cross-cutting research areas illustrate the broader trend.

Scientists have implicated "free radicals" as culprits in brain damage from stroke and trauma, as well as neurodegenerative diseases like ALS, Parkinson's and Alzheimer's, and even infections that affect the brain. Free radicals are highly reactive chemicals that are normal byproducts of energy metabolism, but can damage cells if produced in excess or improperly controlled. This year scientists discovered that patients with a type of inherited ataxia, a movement disorder, had abnormal levels of a vitamin-like substance called coenzyme Q10, which helps protects cells from free radicals. When researchers provided coenzyme Q10 supplements, the patients responded with improved coordination, increased strength and less frequent seizures. Another research team demonstrated in a clinical trial that the drug allopurinol, chosen

to help scavenge free radicals, helps protect the brains of high-risk infants undergoing heart surgery. Several other disease mechanisms repeatedly come into play in many disorders, including excitotoxicity from excessive release of normal brain signaling chemicals, abnormal calcium handling within cells, aggregation of proteins, and activation of "cell suicide" programs. Each of these provides targets for developing preventive and therapeutic strategies that may be widely applicable.

Just as common disease mechanisms help us confront the staggering variety of neurological disorders, there are therapeutic strategies that may apply to many diseases. Gene therapy is deceptively simple in concept, but difficult in practice. The complexities of working with nerve and muscle cells compound the problems. However, scientists have shown promising results in fixing or replacing defective genes in animal models of inherited disorders such as Duchenne muscular dystrophy, and research is demonstrating the potential of gene therapy even in non-inherited disorders, for example, by coaxing cells to make the nerve cell survival factor GDNF or the neurotransmitter dopamine in animals with Parkinson's-like disorders. Stem cells likewise present broad promise. For many years NINDS has supported pioneering research on animal and adult human stem cells, including therapeutic studies in animal models of stroke, spinal cord injury, Parkinson's disease, muscular dystrophy, and inherited metabolic disorders. In the past year, we have seen blood-derived cells convert into nerve-like cells, neural progenitor cells harvested from human brain tissue after death, and stem cells persuaded to become dopamine-secreting nerve cells needed in Parkinson's disease or insulin-secreting cells lacking in diabetes. We are intensifying research on all types of stem cells, as we initiate the study of human embryonic stem cells in accordance with the President's policy announced last August.

Stem cells and gene therapy may have captured the public's attention, but other therapeutic approaches are also promising. Deep brain stimulation (DBS) with implanted electrodes has helped some people with essential tremor and Parkinson's disease and may be more widely applicable to epilepsy, dystonia, pain, and depression. NINDS is building on the expertise of its neural prosthesis program, which helped develop the technology necessary for DBS over the last 30 years, to improve DBS. The Institute is also expanding its drug development efforts to capitalize on the growing understanding of disease at the molecular level. These efforts include high-throughput screening and testing of drugs approved by the FDA for other purposes.

The remarkable progress in understanding the fundamental biology of the brain, of course, is the foundation supporting studies of the common mechanisms of disease and the development of new preventive and therapeutic strategies. Genetics provides one unifying theme, often revealing the first clues to disease processes and yielding animal models for studying disease and testing treatments. The burgeoning research on brain plasticity–how the brain adapts to experience and the environment–may teach us how to

encourage adaptive plasticity to foster recovery from stroke and trauma, and also how maladaptive plasticity contributes to chronic pain and dystonia.

PLANNING AND ENABLING RESEARCH

Motivated by scientific opportunity, enabled by budget increases, and guided by strategic and disease specific planning efforts, NINDS is taking a more active role in directing research. The NINDS strategic planning process began in 1998 and drew upon the nations' leading scientists and physicians, the public and Institute staff. The effort coalesced around cross-cutting themes of neuroscience and resulted in the *NINDS Strategic Plan: Neuroscience at the New Millenium* which has provided a framework for the Institute's activities. These include intensified efforts, through workshops, grant and contract solicitations, and other means as appropriate, that target gene discovery, gene therapy, microarray technology, drug screening, stem cells, deep brain stimulation, pediatric neurology, and common mechanisms of disease, such as mitochondrial dysfunction and protein aggregation.

As NINDS testified last year, the strategic planning process also engendered an increased emphasis on clinical trials, prompted by the opportunities arising from neuroscience research and building on extensive NINDS experience in clinical trials for stroke and other diseases. Ongoing trials range from pilot studies to large phase III efforts, focus on prevention and on treatment, and test interventions that run the gamut, including drugs, surgery, gene therapy, deep brain stimulation, hormone therapy, tissue transplantation, hypothermia, transcranial magnetic stimulation, radiosurgery, behavior modification, and diet, as well as rehabilitation methods. A partial list of disorders being addressed in trials includes: AIDS, ALS, brain tumors, cerebral palsy, attention deficit hyperactivity disorder, brain trauma, epilepsy, Turner syndrome, Parkinson's disease, Lyme disease, migraine, sleep disorders, dystonia, hereditary ataxias, multiple sclerosis, pain, and stroke. Clinical trial results published during the past year report effective immunotherapy for the symptoms of stiff person syndrome - a rare movement disorder; successful field delivery of emergency care for seizures; clinical benefit of enzyme therapy for Fabry disease; improved management of chronic tension headache with added behavior modification; information regarding estrogen hormone-replacement therapy for women for secondary stroke prevention; and improvements in preventing stroke. To complement the clinical trials program, NINDS is developing a comprehensive program to expedite translational research. Translational research bridges from fundamental discoveries about the brain and disease, and rapidly accumulating results in animal models of diseases such as muscular dystrophy, ataxias, ALS, Alzheimer's, Parkinson's, Huntington's, and many others, to the identification of specific agents to be examined in clinical trials of safety and effectiveness.

NINDS health disparities and disease-specific planning efforts build on the foundation of the strategic planning process. The NINDS is implementing research

priorities in stroke, neuroAIDS, epilepsy, pain, and cognitive and emotional health in minorities, and in infrastructure and partnership development in minority institutions. NIH has reported separately to Congress, as directed, about progress in implementing the *Parkinson's Disease Research Agenda* and the January 2002 Consortium meeting. The Agenda represents the most concerted attack NINDS has undertaken against any disease, from basic studies of brain mechanisms through large clinical trials, including efforts to refine existing therapies and to develop new strategies on the frontiers of medicine, such as stem cells, deep brain stimulation, and gene therapy. Among the many facets of this program, the Institute is embarking on a large clinical trial to test drugs that actually slow the course of the disease, rather than merely lessening symptoms.

Other disease-specific planning and implementation efforts are, or will soon be, underway. In March 2000, a landmark conference, "Curing Epilepsy: Focus on the Future," began a process through which epilepsy researchers, patient advocates, and NINDS staff formulated "benchmarks" for epilepsy research, and developed a process to engage the entire epilepsy research community in attaining those goals. NINDS has also reported separately to Congress on this effort, as requested. Major NINDS planning efforts in brain tumor and stroke are following the *Progress Review Group (or PRG)* model developed by the National Cancer Institute; the brain tumor effort in direct collaboration with NCI. In each PRG, more than 100 scientists and representatives of voluntary groups assess the current state of the science and identify future needs and opportunities. The Institute is also undertaking planning efforts in muscular dystrophy and tuberous sclerosis research in the coming year. NINDS is coordinating NIH efforts to implement the *DHHS Bovine Spongiform Encephalopathy (BSE)/ Transmissible Spongiform Encephalopathy (TSE) Action Plan.* BSE, known as "mad cow" disease, is one of the TSEs that pose a potential threat to the public health and economy, and the HHS plan includes surveillance, protection, research and oversight activities. It is important to emphasize that NINDS is also continuing to hold workshops focused on a wide range of specific disorders, such as dystonia, congenital muscular dystrophy, familial dysautonomia, pediatric neurotransmitter diseases, and Joubert syndrome. These meetings, and the ongoing informal interaction among NINDS professional staff, the research community, and disease advocates, catalyze research, while informing the Institute where specific solicitations or other actions may be warranted. Finally, unsolicited grants continue to be the backbone of NINDS research efforts. The collective wisdom of scientists and physicians throughout the nation is especially suited to confronting the broad spectrum of neurological disorders and the scope of science that is essential to progress.

In conclusion, it would be a disservice to patients and families to promise when cures will become available, because medical progress is notoriously difficult to predict. Yet researchers are cautiously optimistic that, by recognizing cross-cutting areas of scientific opportunity, while maintaining a continuing focus on the unique aspects of each disease, we are moving toward an era when curing or preventing neurological disorders will become commonplace. Thank you.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Anthony S. Fauci
National Institute of Allergy and Infectious Diseases

on

Fiscal Year 2003 President's Budget Request
for the National Institute of Allergy and Infectious Diseases

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) for Fiscal Year (FY) 2003, a sum of $3,999,379,000, which reflects an increase of $1,456,933,000 over the comparable Fiscal Year 2002 appropriation. The NIAID budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIAID's second annual performance report, which compared our FY 2001 results to the goals in our FY 2001 performance plan.

OVERVIEW OF NIAID

NIAID supports and conducts basic and applied research to better understand, treat and prevent infectious, immunologic, and allergic diseases. For more than fifty years, NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world. The scope of the NIAID research portfolio has expanded considerably in recent years in response to new challenges such as bioterrorism; the emergence or re-emergence of diseases such as the acquired immunodeficiency syndrome (AIDS), West Nile fever, dengue, malaria and tuberculosis; and the increase in asthma among children in this country. The growth of NIAID programs also has been driven by unprecedented scientific opportunities in the core NIAID scientific disciplines of microbiology, immunology, and infectious diseases. Advances in these key fields have led to a better understanding of the human immune system and the mechanisms of infectious and immune-mediated diseases.

RESPONDING TO THE THREAT OF BIOTERRORISM

The final four months of 2001 were among the most extraordinary -- and tragic -- in American history. The September 11 attacks on the World Trade Center and Pentagon have transformed society in ways that we are only now beginning to discern. Superimposed on that tragedy were the first recorded cases of anthrax in the United States to result from an intentional human act. Of 18 confirmed anthrax cases associated with bioterrorism in the eastern United States in 2001, 11 individuals suffered the inhalational form of the disease; 5 of these people died.

Homeland defense is a multifaceted endeavor. Defense against and response to bioterrorism is a critical component of homeland defense, and our ability to detect and counter bioterrorism depends to a large degree on the state of biomedical science. As the lead agency at NIH for infectious diseases and immunology research, NIAID has developed a *Strategic Plan for Counter-Bioterrorism Research*, as well as a detailed *NIAID Counter-Bioterrorism Research Agenda*, with short-, intermediate-, and long-term goals. The *Strategic Plan* and *Research Agenda* stress two over-arching and complementary components: basic research into agents with bioterrorism potential and the specific and non-specific host defense mechanisms against those agents, and applied research with pre-determined milestones for the development of new or improved diagnostics, vaccine and therapies. We focus on research in six key areas:

Microbial Biology. Research into the basic biology and disease-causing mechanisms of pathogens underpins all our efforts to develop interventions against agents of bioterrorism. NIAID supports research to better understand the factors that influence the virulence and invasiveness of a pathogen, as well as those that determine antibiotic resistance.

An important new tool in understanding all microbes is our ability to rapidly obtain microbial genome sequence information, including that of potential bioterror agents. Many such agents have already been sequenced; others, including different strains of *Bacillus anthracis*, the anthrax bacterium, are in the process of being sequenced. These efforts promise to facilitate the discovery of new medical interventions.

Host Response to Microbes. In order to develop potent, safe, and effective vaccines, accurate diagnostics, and immunotherapeutics against microbes that may be used as bioterrorist agents, research has been accelerated to improve our understanding of the complex parameters of two components of the human immune system: innate and adaptive immunity.

Vaccines. NIAID has bolstered research efforts on vaccines against many of the infectious agents considered to be bioterrorism threats, with an eye toward generating

products that are safe and effective in civilian populations of varying ages and health status. For example, a three-tiered strategy for smallpox vaccine research has been developed. In the near-term, a clinical trial at several NIAID Vaccine and Treatment Evaluation Units suggests that it is possible to "stretch" the 15.4 million available doses of licensed smallpox vaccine 5- or 10-fold by dilution. A concurrent initiative is the development of a new smallpox vaccine: a safe, sterile product grown in cell cultures using modern technology. This vaccine will be rapidly tested in human clinical trials; more than 200 million doses will be produced and delivered to the federal government by the end of 2002. In the long-term, basic research promises to provide a third generation of smallpox vaccines that could be used in all segments of the population, including pregnant women and people with weakened immune system. Additional bioterrorism vaccines also are in development. For example, a new anthrax vaccine, based on a bioengineered component of the anthrax bacterium called recombinant protective antigen (rPA), will soon enter human trials. On the NIH campus, researchers at the NIAID Dale and Betty Bumpers Vaccine Research Center have developed a DNA vaccine that protected monkeys from infection with Ebola virus, and that will soon be tested in human volunteers.

Therapeutics. NIAID therapeutics research focuses on the development of new antimicrobials and antitoxins, as well as the screening of existing antimicrobial agents to determine whether they have activity against organisms that might be employed by bioterrorists. For example, in collaboration with DOD and with support from CDC, NIAID has rigorously screened a large number of antiviral drugs against smallpox-related viruses. One of these agents is an antiviral drug called cidofovir, which is approved by the Food and Drug Administration (FDA) for treating certain AIDS-related viral infections. Cidofovir has shown potent activity against poxviruses related to smallpox in test tube studies and in animal models. NIAID has taken the lead in developing a protocol that would allow cidofovir to be used in emergency situations for the treatment of smallpox. Concurrently, other anti-smallpox agents are being investigated.

Diagnostics. The overall goal of NIAID bioterrorism research on diagnostics is to establish methods for the rapid, sensitive, and specific identification of natural and bioengineered microbes as well as the determination of the microbe's sensitivity to drug therapy. These scientific advances will allow health care workers to diagnose and treat patients more accurately and quickly.

Research Resources. Basic research and the development of new vaccines, therapeutics, and diagnostics depend on the availability of research resources, such as genomics/proteomics information, appropriate animal models, standardized reagents, and appropriate laboratory facilities. Among many initiatives, NIAID plans to accelerate training of investigators specializing in bioterror agents, establish the first four to seven of what will be ten regional Centers of Excellence for Bioterrorism and Emerging

Diseases Research, develop a centralized research reagent repository, and expand the national bioterrorism research infrastructure. The latter will include the construction/renovation of BioSafety Level (BSL) 3-4 laboratories, necessary to work with the most dangerous pathogens.

SPIN-OFFS OF BIOTERRORIM RESEARCH FOR OTHER DISEASES

We anticipate that the large investment in research on counter-bioterrorism will have many positive "spin-offs" for other diseases. The planned NIAID research on microbial biology and on the pathogenesis of organisms with bioterror potential will certainly lead to an enhanced understanding of other more common and naturally occurring infectious diseases that afflict people here and abroad. In particular, the advancement of knowledge should have enormous positive impact on our ability to diagnose, treat and prevent major killer-diseases such as malaria, tuberculosis, HIV/AIDS, and a spectrum of emerging and re-emerging diseases such as West Nile fever, dengue, influenza, and multi-drug resistant microbes. Furthermore, and importantly, the NIAID research agenda on counter-bioterrorism will greatly enhance our understanding of the molecular and cellular mechanisms of the innate immune system and its relationship to the adaptive immune system. This clearly will help in the search for new ways to treat and prevent a variety of immune-mediated diseases such as systemic lupus erythematosus, rheumatoid arthritis and other autoimmune diseases. In addition, new insights into the mechanisms of regulation of the human immune system will have positive spinoffs for diseases such as cancer, immune-mediated neurological diseases, allergic and hypersensitivity diseases, as well as for the prevention of rejection transplanted organs.

VACCINE DEVELOPMENT

Vaccine research, so important to our preparedness against future bioterrorism attacks, has long been a cornerstone of NIAID research. NIAID-supported research has led to the development of many new and improved vaccines that are now widely used; these vaccines have saved literally millions of lives and prevented untold illness and disability from infectious diseases. Success stories include the development of vaccines against Haemophilus influenzae type b, pertussis, chickenpox, pneumococcal disease, and hepatitis A and B. NIAID has three broad goals in vaccine research: identifying new vaccine candidates to prevent diseases for which no vaccines currently exist; improving the safety and efficacy of existing vaccines; and designing novel vaccine approaches, such as new vectors and adjuvants. To speed these efforts, NIAID has made a significant investment in the growing field microbial genomics, and has funded the genomic sequencing of more than 60 medically important microbes. Approximately 20 of these projects have been completed, including the bacteria that cause tuberculosis, gonorrhea, chlamydia, cholera, the parasite that causes malaria, as well as the mosquito that transmits malaria. The availability of the genomic sequences of these and other

organisms will facilitate the identification of a wide array of new antigens for vaccine targets.

One of the important challenges for the 21st century is the development of safe and effective vaccines for the three greatest microbial killers worldwide: HIV/AIDS, malaria, and tuberculosis. These three diseases account for one-third to one-half of healthy years lost in less developed countries. NIAID has a robust portfolio of vaccine research and development for these and other diseases of global importance.

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

Despite recent progress in treatment and prevention, human immune deficiency virus (HIV) disease and AIDS continue to exact an enormous toll throughout the world. An estimated 40 million people are living with HIV/AIDS, and another 22 million people with HIV/AIDS have died. More than 95 percent of these infections and deaths have occurred in developing countries, most of which are also burdened by other significant health challenges. In these nations, HIV/AIDS threatens not only human welfare, but social, political and economic stability as well. In the United States, approximately 850,000-950,000 people are living with HIV/AIDS; approximately 450,000 deaths among people with AIDS had been reported to the CDC as of the end of 2000. The rate of new HIV infections in this country has reached an unacceptable plateau of 40,000 per year, with minority communities disproportionately affected.

In the United States and other western countries, potent combinations of anti-HIV drugs (highly active antiretroviral therapy or "HAART") have dramatically reduced the numbers of new AIDS cases and AIDS deaths. Meanwhile, the toll of AIDS has accelerated elsewhere in the world, especially in poor countries where expensive HAART regimens are beyond the reach of all but a privileged few. Fortunately, this disparity in access to life-saving medications may be changing. Building on the research infrastructure NIAID has helped establish in Africa and elsewhere in the developing world, we are actively working with our international colleagues to link the provision of anti-HIV therapy to efforts in prevention research, with the goal of facilitating a comprehensive approach to the AIDS pandemic in poor countries. Concurrently, NIAID-supported investigators are testing a diverse range of HIV prevention and vaccine strategies. Prevention efforts in our country and abroad focus on several key areas, including behavioral modification, interventions to prevent mother-to infant transmission of HIV, and the development of topically applied microbicides that women could use to protect themselves against HIV and other sexually transmitted pathogens. Several vaccine candidates have recently shown remarkable promise in tests in non-human primates. The best candidates are rapidly being moved into human clinical trials at sites of NIAID's HIV Vaccine Trials Network in the United States and abroad, and at the NIAID Vaccine Research Center.

RESEARCH ON IMMUNE-MEDIATED DISEASES

NIAID-funded research in basic and clinical immunology has led to many promising approaches for treating individuals with immunologic conditions such as multiple sclerosis, type I diabetes and asthma. Researchers are 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. The NIAID-supported Immune Tolerance Network an international consortium of approximately 50 research groups, now has 16 clinical trials that are enrolling patients or will do so soon, in areas such as islet transplantation (for diabetics), kidney transplantation, autoimmune diseases, and asthma and allergic diseases.

For the past decade, NIAID also has focused on reducing the significant and growing burden of asthma among inner-city minority children. The current Inner-City Asthma Study has investigated novel interventions to improve the health of inner-city children with asthma. One approach, called a physician feedback intervention, involves periodic reports to the child's doctor about the status of the child's asthma. These reports, generated from bi-monthly phone interviews with parents, recommend changes in the child's treatment regimen according to National Heart, Lung, and Blood Institute (NHLBI) guidelines, if warranted. Another method is an environmental intervention that involves identifying and removing asthma triggers such as cigarette smoke or cockroaches from the child's home. Both interventions are reducing health care utilization, and the children receiving the environmental intervention gained an additional three weeks of symptom-free days during the intervention year. We are working to make such interventions available nationwide.

CONCLUSION

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Marvin Cassman
National Institute of General Medical Sciences

on

Fiscal Year 2003 President's Budget Request
for the National Institute of General Medical Sciences

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Institute of General Medical Sciences (NIGMS) for FY 2003, a sum of $1,881,378,000, which reflects an increase of $154,911,000 over the comparable Fiscal Year 2002 appropriation.

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's third annual performance report, which compared our FY 2001 results to the goals in our FY 2001 performance plan.

Today, 40 years since NIGMS was established, we can look back and reflect on the many accomplishments of the Institute. NIGMS-funded research has played a major role in building a strong foundation for all of biomedicine, producing a steady stream of research advances in a spectrum of disciplines. These advances have emerged from fundamental research in very basic areas like genetics, chemistry, and cell biology; and from more applied areas of science such as the body's response to medicines and to injury caused by trauma or burns.

A GOOD MODEL

In our anniversary year, I think it is fitting to showcase some of the medical benefits that have grown out of NIGMS's strong investment in supporting basic research--especially that obtained from studies with non-mammalian model organisms. Years of basic research with model organisms continue to yield valuable information, including important medical insights. An explosion of new discoveries rooted in basic investigations of the biology of the common baker's yeast are paving the way for effective means to treat infections caused by microbial cousins of this common fungus, including the potentially dangerous yeast *C. albicans*. This species of yeast causes

vaginal and gut infections and can cause life-threatening problems for people with weakened immune systems, such as AIDS patients or transplant recipients.

Other recent medical advances stemming from studies with yeast include several important research findings on biofilms, specialized "mats" of bacteria or fungi that tend to be particularly resistant to medical attack. Biofilms, which account for everything from dental plaque to unsightly toilet bowl stains, also thrive in the clogged airways of people with cystic fibrosis, where they create tremendous problems. NIGMS-funded research with baker's yeast has shown that these ordinary fungi can be made to form a biofilm structure, providing scientists with a robust, inexpensive, and safe system to study the properties of biofilms as well as test drugs to block the formation of biofilms.

There is no question that, for years to come, scientists will continue to relish the versatility and economy of baker's yeast, properties that make this model organism an extraordinarily resilient and productive research tool.

I would like to move on to an exciting story about a team of scientists who are getting some old drugs to try new tricks. Over time, the group's research findings on the chemical and physical properties of certain enzymes and other proteins involved in basic metabolism led to the idea that a certain class of chemicals may live a dual life. These so-called "bisphosphonates," the researchers discovered, are capable of blocking an enzyme critical to the livelihood of parasites, the organisms that cause malaria and other infectious scourges. But the same chemicals can also knock out a human enzyme whose activity breaks down bone during osteoporosis. This multifaceted group of researchers put their heads together and--blending chemistry, biology, and very fast computers--discovered that a key step in parasite metabolism could indeed be knocked out by the anti-osteoporosis medicines Fosamax®, Actonel®, and Aredia®. Their new research shows that fairly low concentrations of these FDA-approved drugs can do away with parasites while sparing human cells. The scientists are now testing the drugs in animal models of the diseases and so far have obtained cures--in mice--of certain types of leishmaniasis, another disease caused by parasites. If the medicines work well in animal models, testing the drugs in people could occur relatively quickly, since the medicines have already been approved for other uses, and therefore have already been tested for safety in people.

Other fundamental lines of inquiry have led to unexpected practical benefits in treating disease. Ten years of intense analysis of the properties and functions of a plant enzyme led to the discovery that the active ingredient in the weedkiller Roundup® attacks this particular enzyme. The enzyme, the researchers learned years later, also happens to be present in parasites, fungi, and other microorganisms. From this discovery, the potential medicinal value of interfering with this enzyme came into clear view. Fundamental biophysical studies that show what this enzyme looks like up close have now handed scientists a blueprint for designing chemical compounds to disable the

action of this critical molecule. This research will likely lead to potent new medicines to treat parasites, bacteria, and fungi that cause illness in people.

MEDICINES FROM LAND AND SEA

NIGMS's research investment in chemistry has yielded important medical treatments from the ocean, which can be illustrated by two examples. The first is a poison derived from the venom of a marine snail species called *Conus*. To marine predators, a small molecule produced by *Conus* snails is deadly and serves as a form of defense. But for people with certain forms of chronic pain, this molecule may be extremely helpful in numbing pain that is unresponsive to other methods of pain treatment. Nearly a decade of NIGMS research probing the properties and physiological effects of *Conus* poisons has matured into the discovery and production of the compound Ziconotide. This medicine has completed clinical testing and is awaiting FDA approval. If approved, Ziconotide will be the first marine organism-based pharmaceutical product. Due to the fact that so many *Conus* varieties exist in nature, and that each snail produces many different venoms, the pharmaceutical potential of this humble organism seems vast. Indeed, a number of other promising *Conus*-derived molecules are in the drug development pipeline for a range of clinical applications, including treatment for burn pain, eye pain, postoperative surgical pain, and certain nervous system disorders.

A second example of medicine from the sea is a chemical called "Et743," which was originally discovered in a Caribbean sea squirt called *Ecteinascidia turbinata.* Scientists have shown that Et743 is an extremely powerful killer of cancer cells, particularly soft-tissue sarcomas, and the drug is now in late-stage clinical testing. Despite the medical potential of Et743, a severe shortcoming early on was its very limited availability in nature. NIGMS-funded chemists made an important step in extending the utility of this chemical by figuring out how to make it easily in the lab, starting with simple materials.

Getting back to land, I want to highlight some medical benefits offered through research with a terrestrial laboratory darling, the ordinary fruit fly. Fundamental research using these tiny red-eyed insects has shed light on many basic features of the development of all of the body parts of embryos, including the development of human embryos. NIGMS-supported scientists discovered a fruit fly gene whose protein product helps fly ovary cells move to where they need to go during the normal process of development of the ovaries. This fly gene is strikingly similar to a human gene that, when misspelled, is overproduced in human breast and ovarian cancers. The work not

only adds to fundamental knowledge about how cells know where to go as they meld together into organs and tissues, but it also provides a useful tool for cancer researchers studying the causes and treatments for breast and ovarian cancer.

Recently, NIGMS-funded genetic research with fruit flies demonstrated that these insects may hold a key to curing a host of different human diseases. One study unearthed 548 fly genes that are so similar to genes involved in 714 different human genetic disorders that the likelihood of the similarity occurring by chance alone is 1 in 10 billion. What this means is that scientists can look for causes and treatments for blindness, cancer, Parkinson's disease, diabetes, and many other disorders using lab fruit flies that are inexpensive and can be bred very quickly. Ultimately, scientists predict that fly genes will play an important role in the study of at least 1,000 of the 5,000 known genetic diseases in people.

RESEARCH TRAINING

NIGMS is proud once again to cite the Nobel Prize-winning work of two of its long-time grantees. Geneticist Dr. Leland Hartwell and chemist Dr. Barry Sharpless each received the Nobel Prize in 2001 for their work on the cell cycle and chemical tools called chiral catalysts, respectively. Such quality scientific research gets done by quality researchers, and a vital component of the NIGMS mission is training the next generation of scientists. NIGMS maintains its leading role at NIH in research training by supporting nearly 44 percent of the predoctoral trainees and roughly 29 percent of all trainees receiving training funds from NIH. In recognition of the interdisciplinary nature of biomedical research today, all of NIGMS's training programs place a strong emphasis on crossing disciplinary boundaries. Nearly half of the NIGMS-funded biotechnology predoctoral fellowship programs, for instance, are centered in engineering departments.

In keeping with its commitment to training a diverse research work force, NIGMS is vigilant to how institutions recruit and retain trainees who are members of underrepresented minority populations. To propel these efforts, NIGMS sponsored a successful workshop in May 2001 at which institutions shared best practices for minority recruitment and retention in their training programs. We are promoting continued sharing via a minority recruitment and retention strategies Web site.

Looking more globally at our minority programs, I want to bring to your attention a few very interesting and fruitful examples of outreach with Native American populations. Together with National Human Genome Research Institute staff, this past year NIGMS staff organized a visit to Diné College on the Navajo Reservation. Staff of the NIGMS Division of Minority Opportunities in Research continue to work tirelessly to motivate, guide, and assist minority institutions, faculty members, and other prospective grantees who are new to the NIH funding system. I would like to highlight one particularly innovative ongoing partnership with the Indian Health Service. Beginning in FY 2001, NIGMS established a collaborative program designed to improve research and research training responsive to the needs of Native American communities. The Native American Research Centers for Health (NARCH) program

supports partnerships between American Indian or Alaska Native tribes and research-intensive institutions.

SPECIAL INITIATIVES

Of course, a key component to providing top-notch training programs is to closely follow the directions in which science takes us, and NIGMS has listened carefully to what the scientific community has to say about what's needed to move science forward. To that end, I am happy to report that NIGMS-funded initiatives aiming to pull together science from different, complementary fields of study are moving ahead. Important progress is being made by researchers in the NIGMS-led NIH Pharmacogenetics Research Network, with four new research teams joining the existing effort in September 2001. Two new teams of scientists joined NIGMS's Protein Structure Initiative, and three multifaceted research groups were awarded large-scale "glue" grants to study how cells communicate via natural sugar molecules, how cells move around the body, and how the body responds to injury caused by trauma and burns.

CONCLUSION

NIGMS remains dedicated to developing and sustaining programs that ensure the advancement of the basic biomedical research that will fuel the discovery of tomorrow's medicines.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Duane Alexander
National Institute of Child Health and Human Development

on

Fiscal Year 2003 President's Budget Request
for the National Institute of Child Health and Human Development

Mr. Chairman and Members of the Committee:

I am pleased to present the FY 2003 President's budget request for the National Institute of Child Health and Human Development (NICHD) of $1,218,112,000 which reflects an increase of $100,870,000 over the comparable FY 2002 appropriation.

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compares our FY 2001 results to the goals in our FY 2001 performance plan.

For almost 40 years the NICHD has conducted research that touches Americans throughout their lives. We seek to ensure that people are able to have the children they want at the time they want them; that women experience pregnancy without complications and suffer no adverse consequences from the reproductive process; that every child is born healthy and wanted; that all children experience healthy physical, cognitive, behavioral, and social development and reach adulthood free of disease and disability and able to fulfill their potential for a productive life; and that people of all ages who experience disability as a consequence of congenital defects, injury, or disease achieve maximum function through the best rehabilitation we can provide. We have a broad mission, and we have a dynamic program of research in all of these areas.

EARLY CHILDHOOD EDUCATION AND SCHOOL READINESS

Reading skills are essential to function in our society. Yet many children, particularly children born in poverty, never learn to read. This inability to read has profound and long term implications for the children in terms of their health, their participation in civic life, and their ability to function in an increasingly complex world. Our research has demonstrated that getting children ready to read before kindergarten is a critical step in actually learning to read. Children need to have a basic understanding that there is a connection between sounds, letters, words and print before and during kindergarten to learn to read by the first grade. Our research has also revealed that the vast majority of students who are poor readers in the first grade

remain poor readers in the fourth grade and that almost all children who are good readers in the first grade remain good readers in the later grades. Early intervention is critical to developing good reading skills and the interventions should start before kindergarten. The NICHD, in cooperation with the NIMH and the Department of Education, is launching a new program to identify the most effective ways to help children develop their learning abilities. The program has a comprehensive focus that includes promoting cognitive, language and early reading and math abilities as well as self regulation skills, social competency, and emotional health. We strongly believe that every healthy child can and must learn to read.

ADVANCES IN MENTAL RETARDATION

Since the NICHD was established, we have made remarkable progress in identifying, treating, and preventing many of the causes of mental retardation. Today, parents do not have to fear phenylketonuria (PKU), congenital hypothyroidism, or Hemophilus influenzae type b meningitis because these major causes of mental retardation have been virtually eliminated. Moreover, other causes of mental retardation such as measles encephalitis, congenital rubella syndrome, and bilirubin encephalophy have nearly disappeared. And we are making progress in learning more about the most common inherited cause of mental retardation – Fragile X syndrome.

NICHD has a long history of supporting research on Fragile X syndrome. In the early 1990s, our research led to the identification of the gene affected in Fragile X, FMR1. Last year, in a unique collaboration between the NICHD, the NIMH and the FRAXA Research Foundation, we funded researchers exploring the neurobiology and genetics of Fragile X syndrome. This year, we will establish three new Fragile X Research Centers to conduct research directly related to the causes, treatment and prevention of Fragile X syndrome.

We are also increasing our research in autism. Within the NIH, five Institutes are members of the NIH Autism Coordinating Committee (NICHD, NIMH, NINDS, NIDCD, and NIEHS). Since this Committee was established a few years ago, the NIH has substantially increased its support of autism research from $22 million in 1997 to more than $55 million in 2001. The Collaborative Programs of Excellence in Autism (CPEAs) are a major focus of our research in autism. The CPEAs, which we fund along with the NIDCD, link more than 2,500 families of people with autism to more than 75 researchers in 26 universities around the country. The CPEA Network in turn is linked to a six-nation European autism consortium. The Network serves as a resource for individuals with autism and their families. The CPEA Network is now studying the world's largest group of well-diagnosed people with autism whose genotype and phenotype are available. NICHD will also join other NIH Institutes in funding at least five new comprehensive Centers of Excellence in Autism Research as required by the Children's Health Act of 2000.

Our Institute is committed to understanding and eliminating the causes of mental retardation. We are equally committed to applying the results of our research to the

elimination of the barriers that people with mental retardation experience. The President's New Freedom Initiative calls for all Americans to be able to realize the dream of equal access to full participation in American society. For people with mental retardation, we came closer to realizing that dream in our collaboration with the Surgeon General on the Conference on Health Disparities and Mental Retardation. This unique conference was planned and carried out with the full participation of people with mental retardation. It resulted in a blueprint that we all can use to reduce these disparities.

MOBILITY FOR ALL

Traumatic injury is the leading cause of death for children and adolescents in the United States. Major advances in medicine and emergency room services have helped children survive their injuries, but many survive with disabilities and long term effects on their quality of life. Their conditions are managed through a variety of rehabilitation interventions such as medications, physical therapy, and adaptive equipment or prostheses. However, we have little information on the effectiveness of many interventions for children. A wide range of developmental events distinguishes the rehabilitation of infants, children, and adolescents from that of adults. Therefore we are establishing a series of clinical trial planning grants in pediatric rehabilitation. Our goal is to assure that infants and children who experience traumatic injury are restored to their maximum function through the best rehabilitation we can provide.

Traumatic brain injury (TBI) is a leading cause of disability among adults. During the last two decades, our understanding of traumatic brain injury has increased dramatically. For instance, we now know that not all neurologic damage occurs at the moment of injury, but evolves over the ensuing minutes, hours and days. We are therefore establishing a multi-center network of clinical sites to evaluate the relationship between acute care practice and rehabilitation strategies and the long term well-being of TBI patients. Our goal is to identify which of the interventions are most likely to result in long term improvements.

PREMATURE BIRTHS

Infants born prematurely have much greater risk of dying in infancy than do other infants. Premature birth puts infants at greater risk for life-threatening infections, for a serious lung condition known as respiratory distress syndrome, and for serious damage to the intestines. The earlier infants are born, the more problems they are likely to face. Some may develop lifelong disabilities, such as blindness, mental retardation, and cerebral palsy. The causes of premature birth remain a puzzle. Physicians have been largely powerless to prevent this serious, and often deadly, complication of pregnancy. Now, however, two groups of NICHD scientists have put many of the puzzle pieces in place and a clearer picture is taking shape.

Recently, NICHD scientists and their colleagues discovered that a surge in a stress hormone may signal the beginning of premature labor. They found that women

who gave birth prematurely had higher levels of the stress hormone than did women who gave birth at full term. They also found that women who had a low level of education, received public assistance, or worked at jobs requiring them to stand or walk for more than six hours a day, also were more likely both to have high levels of the stress hormone and to give birth prematurely. These researchers are now looking for ways to reduce the levels of stress hormone during pregnancy to help prevent premature birth.

Our research is also changing the way we think about prematurity. Traditionally, researchers have believed that premature labor is an accident in which the uterus begins to contract before the unborn infant has reached full term. NICHD scientists have now uncovered evidence that in many cases, the fetus becomes seriously ill and chemically signals the beginning of labor in order to escape a hostile uterine environment. Instead of being an accident, the initiation of early labor may be a means that nature developed to spare mothers and babies from infection. We are now trying to find ways to identify women who have these infections and who may be at risk for premature labor and find successful ways to treat them. We are also exploring why African American women are more likely to give birth prematurely than are women in other ethnic groups. For example, we have discovered that some African American families are more likely to possess variations in the genes that signal rupture of the membranes, the prelude to labor. These variations may make it more likely that labor will begin prematurely.

DECLINE IN SIDS RATES

Since we began a public health campaign eight years ago urging parents and caretakers to place infants on their backs to sleep, we have witnessed a continuous and steady decline in the number of infants dying from Sudden Infant Death Syndrome or SIDS. Provisional data from the CDC show that the SIDS rate has declined by more than 50 percent since the campaign began. This remarkable achievement is a result of the thousands of individuals and the many organizations who have taken part in this national public health education effort.

Although the number of infants who die of SIDS has declined in all ethnic groups, twice as many African American infants die from SIDS as do white infants. To address and help eliminate this disparity, we are working with several national African American organizations including Alpha Kappa Alpha, 100 Black Women, and the Women of the NAACP who are meeting with parents and caretakers in schools, in churches, and in a variety of community settings on the ways to reduce the risks of SIDS. In the last 12 months more than 50 individual workshops have been conducted, and many more workshops are planned in the coming months in our effort to eliminate the disparity in the rate of SIDS.

DRUGS TO IMPROVE THE HEALTH OF CHILDREN AND PREGNANT WOMEN

Until fairly recently, over the counter and prescription drugs that were safe for adults were considered safe for children. However, in addition to being a smaller size,

children's brains, bones, and metabolism are different from those of adults. Many of the drugs that have been shown to be safe and effective for adults have never been tested with children and in fact may behave very differently in children. In 1994 the NICHD established the Pediatric Pharmacology Research Unit (PPRU) network as a resource for testing the safety and effectiveness of drugs for infants, children and adolescents, and immediately began conducting research on drugs that have been inadequately studied. The network consists of a partnership among the NIH, the pharmaceutical industry, and university-based researchers. The PPRU network has grown considerably since the 1997 passage of the Food and Drug Administration Modernization Act. Thus far, the PPRU network has conducted more than 100 studies of drugs in children, including a new anti-diabetic drug. The working group is also developing new and advanced techniques to monitor a child's blood sugar. The PPRU network demonstrates that studies of drugs can be ethically and efficiently conducted in children.

The study of drugs used during pregnancy is another area of significant concern. Surveys reveal that nearly two- thirds of all pregnant women take at least four or five drugs during their pregnancy. Most of these drugs have never received FDA approval for obstetric use. Funds in the FY 2003 request will enable the NICHD to establish a network of Obstetric Pharmacology Research Units (OPRUs) to conduct studies of drugs during pregnancy to assess dose and safety issues in a way that will provide the necessary information for labeling for use in pregnancy.

WOMEN'S HEALTH RESEARCH

In another area of women's health, NICHD has established a Clinical Trials Network in Female Pelvic Floor Disorders and has funded eight sites in this network this year. Each site in the network supports a multidisciplinary team with the expertise, resources, and infrastructure needed to conduct the clinical studies in pelvic floor dysfunction, such as pelvic organ prolapse and incontinence. We are also collaborating with the NIDDK in funding a Urinary Incontinence Treatment Network. Through this array of support of basic and clinical research we hope to discover better ways to prevent and treat pelvic floor disorders.

ANTHRAX VACCINE

Scientists in NICHD's intramural laboratories, using funds provided in the DHHS Bioterrorism Initiative in the last three years, have developed a new approach to a vaccine against anthrax that they believe will require fewer injections, have fewer side effects, and induce better immunity. Funds in the FY 2003 budget request will support clinical trials of this new vaccine.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Paul A. Sieving
National Eye Institute

on

Fiscal Year 2003 President's Budget Request
for the National Eye Institute

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Eye Institute (NEI) for FY 2003, a sum of $631.8 million, which reflects an increase of $49 million over the comparable Fiscal Year 2002 appropriation.

It is my pleasure to testify today as the new Director of the NEI. I am grateful for the opportunity to assume this role during a time of unparalleled growth, progress, and opportunity in biomedical research. The National Eye Institute and the scientists it supports are committed to reducing the threats to our vision and to improving the visual health of our citizens. The research that they perform in this pursuit touches upon every area of scientific endeavor and every facet of the visual system. Vision scientists have advanced our knowledge of and improved treatment for a number of eye diseases during this past year, and they stand ready to seize the new opportunities and meet the challenges that await us in the field of vision research.

RETINAL DISEASE RESEARCH

The retina is the transparent, light-sensitive tissue that lines the back of the eye. Diseases and disorders of the retina and its blood vessels account for much of the blindness and visual disability in this country. In the U.S., the most important of these include macular degeneration, diabetic retinopathy, retinitis pigmentosa and related disorders, retinal detachment, uveitis, and glaucoma.

NEI-supported scientists have made important progress in treating a form of childhood blindness. A genetic disorder called Leber's Congenital Amaurosis (LCA) causes blindness in children by mechanisms similar to those in retinitis pigmentosa. Scientists demonstrated successful gene transfer to restore vision in an animal model of this disease. Treatment was performed by introducing normal copies of the gene to replace the mutated gene. Exciting work lies ahead of us to determine whether this approach has potential as a sight-restoring therapy in humans. It is our best hope that this research will lead to a safe and effective means to restore vision or prevent vision

loss in patients with LCA and provide a roadmap for the development of therapies for people with a variety of similar diseases.

Researchers also released major findings related to the prevention of macular degeneration. The Age-Related Eye Diseases Study, called AREDS, demonstrated that high levels of antioxidant nutrients and zinc reduced the risk of advanced age-related macular degeneration. Other NEI-sponsored scientists continue to conduct laboratory and clinical studies on the developmental, molecular and cellular biology, the molecular genetics, and metabolism of the photoreceptor cells that capture light; the initial neural processing of information that is transmitted to the visual centers of the brain; the pathogenesis of diabetic retinopathy; and a variety of other sight-threatening eye diseases and conditions. The ultimate goal of these studies is to develop effective therapeutic or preventive measures where none currently exist or to improve those treatments that are currently available.

CORNEAL DISEASE RESEARCH

The cornea is the transparent tissue at the front of the eye that plays an important role in refracting or bending light to focus visual images sharply on the retina. Because the cornea is the most exposed surface of the eye, it is especially vulnerable to damage from injury or infection. The leading causes of corneal blindness are herpes simplex virus (HSV) infection and other infections, corneal opacification or clouding, and inherited and degenerative diseases. Recent results from NEI-sponsored studies have provided important information about the spread of HSV and have suggested that rapid systemic treatment may be more effective than topical antivirals in treating acute, primary infections. Scientists have also learned more about the immune mechanisms involved in corneal transplant rejection and have suggested a means to increase transplant success.

The NEI supports a variety of other laboratory and clinical studies, including: the regulation of genes that express proteins unique to corneal tissue; investigation of the use of adult corneal stem cells to treat corneal damage due to disease or injury; the mechanisms that maintain corneal hydration and transparency; improvement in the diagnosis and treatment of dry eye; the physiologic basis for autoimmune disease involving the cornea; and corneal wound healing. These studies should ultimately improve our ability to limit or prevent damage to corneal clarity caused by injury, infection, or other disease processes.

CATARACT RESEARCH

A cataract is an opacity of the eye's normally clear lens that interferes with vision. Cataract may develop at any time during life, although it is most often associated with advancing age. In addition to aging, cataract may be a consequence of diabetes and other

metabolic disorders, trauma, exposure to ionizing radiation, or it may be inherited. Although cataract treatment in this country is one of the most successful of all surgical procedures, development of non-surgical approaches to preventing or treating cataracts remains a research priority.

NEI investigators have recently reported that women on estrogen replacement therapy are less likely to develop cataracts. Additionally, scientists have found that a subunit of a major protein component of the lens is highly effective in protecting cells from stress-induced cell death but may become overwhelmed, leading to cataract formation. These results suggest additional avenues of research that may lead to non-surgical therapies to prevent or delay cataract formation. NEI-sponsored research continues on the development and aging of the normal lens of the eye; the identification of the molecular and cellular components that maintain the transparency and proper shape of the lens; the control of lens cell division and differentiation; and the impact of continual oxidative insult on the lens.

GLAUCOMA RESEARCH

Glaucoma leads to blindness from damage to the optic nerve of the eye. Glaucoma is often, but not always, associated with increased pressure within the eye caused by inadequate drainage of aqueous humor, the fluid within the eye that nourishes the cornea and lens. Although glaucoma is primarily a chronic disease of aging, it may occur at any age. It can occur as a primary disorder or it can be secondary to other ocular or systemic conditions. Glaucoma is a major health problem and the number one cause of blindness in African-Americans. Glaucoma research is a primary focus for NEI's research on health disparities. More than two million Americans have definite glaucoma and it is estimated that another two million are unaware that they have the disease. Nearly 120,000 are blind from this disease.

In the past few weeks, NEI-funded investigators identified a new gene mutation on chromosome 10 that caused a form of adult-onset glaucoma. The gene codes for a protein that normally protects nerve cells from damage. Scientists have also recently identified a molecular marker of glaucoma in the trabecular meshwork, which forms the tissue that regulates the exit of aqueous humor from the eye. This same substance is the earliest marker for the buildup of fatty deposits in the linings of blood vessels damaged by high blood pressure. Other markers that are usually associated with oxidative stress and inflammatory reactions were also identified in cells from glaucoma patients. Such studies offer insights and hope for new and more effective therapeutic interventions.

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING RESEARCH

Childhood vision loss most frequently results from strabismus, a misalignment of the eyes and the development of amblyopia, or lazy eye. Strabismus results in diseases

in which visual processing is abnormal. Amblyopia can result from this misalignment or from unequal refraction between the eyes. Research on strabismus and amblyopia encompasses a broad range of clinical and laboratory studies on the structure and function of the neural pathways from the retina to the brain, the central processing of visual information, visual perception, the control of ocular muscles, and refractive errors.

Important new results from the Amblyopia Treatment Study are being released March 13. This study began recruiting patients in April 1999 to compare two different treatments for amblyopia–eye patching or administration of a single eye drop of atropine per day. These exciting findings will change clinical practice in this country. NEI research support continues for a broad range of other preventative, therapeutic and laboratory studies that are concerned with the development and function of the neural pathways from the eye to the brain; wiring of the visual system of the brain during the young years of development; the central processing of visual information; visual perception; optic neuropathies; eye movement disorders; and the development of myopia.

HEALTHY PEOPLE 2010

Healthy People 2010 is a national initiative to prevent disease and promote health issues sponsored by the U.S. Department of Health and Human Services. Vision objectives, codified as *Healthy Vision 2010*, are highlighted in this initiative. The NEI coordinates the workgroup activities designed to accomplish these objectives. This vision focus area addresses visual impairment due to eye disease and refractive error; regular eye examinations for children and adults; vision screening for pre-school children; and injury prevention. Initial activities include collecting baseline data on eye disease prevalence, so that progress can be monitored in treating the visual disabilities that lead to low vision and impair the productivity and quality of life of our citizens.

HEALTH EDUCATION AND COMMUNICATION

The National Eye Health Education Program (NEHEP) was mandated by Congress and implemented by the NEI to increase awareness among health care professionals and the public of scientifically based health information that can be applied to preserving sight and preventing blindness. NEHEP works through its partnership of over 60 professional and voluntary organizations to implement three formal education programs covering glaucoma, diabetic retinopathy, and low vision.

The newest of these programs is the Low Vision Education Program, designed to increase awareness of low vision and its impact on quality of life. As a part of this program, the NEI launched a multi-year nationwide shopping center tour of THE EYE SITE – A Traveling Exhibit on Low Vision. The exhibit consists of five colorful kiosks and features an innovative interactive multimedia touchscreen program. The exhibit is

targeted to all people over age 65, and Hispanics and African Americans of any age. These groups, their families, and friends are the primary audience for the exhibit.

Another NEHEP program theme highlights a new Medicare benefit for glaucoma detection, which became effective in January. The Medicare benefit includes coverage of a dilated eye examination with an intraocular pressure measurement for people at highest risk of developing the disease, including African Americans over age 50, people with diabetes and those with a family history of the disease. This new effort is being coordinated with other Federal agencies, including the Center for Medicare and Medicaid Services.

GOVERNMENT PERFORMANCE AND RESULTS ACT

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compared our FY 2001 results to the goals in our FY 2001 performance plan.

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Kenneth Olden
National Institute of Environmental Health Sciences

on

Fiscal Year 2003 President's Budget Request
for the National Institute of Environmental Health Sciences

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) for FY 2003, a sum of $619,769,000, which reflects an increase of $48,290,000 over the comparable Fiscal Year 2002 appropriation. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compared our FY 2001 results to the goals in our FY 2001 performance plan.

INTRODUCTION

Although most of the visible environmental problems of the 1950s and 1960s have been ameliorated, massive quantities of toxic agents are still polluting our environment. This includes chemicals that are known to be rodent and human carcinogens and neuro-, immuno-, or developmental toxins. Whether current levels of exposure to these agents are contributing to the high or increasing incidence of cancer, Parkinson's and Alzheimer's Disease, asthma, autism, learning disabilities, diabetes, or other complex disorders is a matter of considerable concern. Finding answers to these questions has been a slow and difficult process. The traditional methodologies available to environmental health researchers have not been adequate to elucidate the intricate gene-environment interactions involved in the development of complex diseases.

Today, the environmental health sciences stand on the threshold of new and exciting opportunities. The knowledge and technologies spun by the Human Genome Project has unshackled this important discipline and created unprecedented technological opportunities to advance our understanding of environmentally-associated toxicities and diseases. By using a combination of new technologies (genomics, proteomics, and metabonomics), one can achieve an integrative view of gene-environment interaction at the level of the whole organism.

To exploit the disease prevention promise of these technologies, NIEHS has targeted three critical areas of research: (1) identification of the suite of gene-environment interactions involved in the development of the major diseases, (2) development of public health or medical prevention/intervention strategies, and (3) development of mechanisms to translate knowledge and technology into the practice of preventive and clinical medicine. By investing in these areas

of research, NIEHS expects to be a major contributor to one of the most important functions of government – the protection of human health.

I will briefly describe three technologically-driven initiatives that represent major investments for the NIEHS, and have potential for preventing disease, making sound environmental health policy decisions, and reducing the time and costs associated with assessing the toxicity or carcinogenicity of chemical and physical agents in our environment.

SEARCH FOR ENVIRONMENTAL SUSCEPTIBILITY GENES

Throughout life, human and other organisms are subjected to environmental insults on a continual basis. As a result, sophisticated metabolic pathways have evolved to buffer against toxic injury. Collectively, these buffering pathways or mechanisms have been referred to as the "environmental response machinery." All human genes, including those that code protein components of the environmental response machinery, are subject to genetic variability that can result in outright failure or altered efficiency in a buffering or protective mechanism.

Although reference is made to the human genome, the concept of a single genome is misleading. Each individual's genetic makeup, with the exception of identical twins, is unique. While the genomes of individuals are 99.9% identical, the 0.1% variation leaves considerable room for individual differences among the approximately three billion nucleotide base pairs that make up the human genome. The variation in gene structure among individuals is known to play a significant role in disease development by increasing or decreasing sensitivity to environmental insults.

To date, very few environmental susceptibility genes have been identified, but with improvements in methods of gene discovery and genotyping, large-scale studies of the genetic basis for susceptibility to environmental exposures are now practical. Therefore, NIEHS initiated a search for such environmental susceptibility genes approximately three years ago with the announcement of the Environmental Genome Project (Science 278: 569-570; Nature Genetics 18: 91-93), by contracting with the genome sequencing laboratories developed by the Human Genome Project. The questions being addressed by the genome discovery project include: (1) Which of the genes coding for proteins involved in buffering against environmental insults vary structurally among individuals, (2) What is the relative distribution of the various forms of the genes in the U.S. population, and (3) What are the consequences of the genetic alterations with respect to toxic injury or susceptibility to environmental exposures? To date, we have completed the search for functional variations in 104 of the 544 genes initially targeted for analysis. This has been done in a sufficient population sample size so that we can be reasonably certain that variations discovered are representative of the U.S. population. However, I should stress that the 544 genes examined in this study do not represent all, or even most, of the environmental susceptibility genes in the human genome; most are yet to be discovered. In fact, NIEHS is collaborating with the National Human Genome Research Institute and other Institutes in the Single Nucleotide Polymorphism discovery and the Haplotype-Mapping projects to uncover other susceptibility genes.

I should also emphasize that genes are not the only factors that contribute to differences in susceptibility to environmental exposures; age or stage of development, behavior, and general health or nutritional status can have a spectacular influence. In the interest of time, these issues will not be addressed here, but they are among the top investment priorities of the NIEHS.

TOXICOGENOMICS

The vast majority of synthetic and natural chemicals in our daily environment have not been thoroughly screened for toxicity ("Toxic Chemicals," Environmental Defense Fund, 1993). Also, the demand for toxicity assessment has increased dramatically over the past decade because of the rapid evolution of drug discovery science and the build-up of chemical and physical pollutants in the environment resulting from activities of the increasing human population. Thus, more efficient and cost-effective toxicity screening methods must be developed. The conventional approaches of exposing laboratory animals to high doses of single chemicals are too slow, too expensive, use too many animals, and are not very informative with respect to mechanisms of toxicity.

Toxicogenomics is a new discipline, spun from the Human Genome Project, that merges toxicology with new technologies for analysis of genes (genomics), proteins (proteomics), and metabolites (metabonomics) derived from cells, tissue extracts or body fluids. This field of endeavor was formally inaugurated when NIEHS announced the development of the National Center for Toxicogenomics in November 2000 (Science 289: 536-537; Pollack, Andrew, The New York Times, 28 November 2000). The Center consists of an intramural laboratory and five university-based programs. Program coordination and database management are handled by the intramural component.

This approach to assessment of toxicity was made possible by development of the capacity to array thousands of DNA fragments, corresponding to specific genes, on matrices and hybridization with mRNA or cDNA. Using this approach to profile mRNA expression patterns, one can determine which genes are turned on or off by exposure to specific environmental agents. However, the mRNA product of a single gene can be sliced or processed to give rise to several proteins or peptides. Therefore, protein and metabolite analyses are necessary to understand the mechanisms and pathways involved in the development of disease or toxicity.

Toxicogenomics is a promising technology, but one that will take a while to achieve the potential public health and economic benefits. Toxicologists must develop a knowledge base to discriminate between adaptive or pharmacological responses and toxicological effects, as virtually any change in the environment will influence the expression of many genes. Also, signature patterns must be correlated with conventional indices of toxicity. So, hundreds of chemicals and many experimental variables will need to be examined before we will know its full impact.

MOUSE GENOMICS CENTERS

Fortunately, almost every human gene appears to have a counterpart in the mouse, opening the possibility of constructing special mouse models containing the specific variations (polymorphisms) identified in the Environmental Genome Project. Such models are now being developed by use of gene "knock-out" and "knock-in" technology in several university-based Centers established for this purpose by NIEHS in 2001. These models will be made available to researchers upon request to investigate the relationship between particular genotypes and environmental exposures and diseases.

PUBLIC OUTREACH AND TRANSLATION OF RESEARCH

It is becoming increasingly important to get consumers more intimately involved and informed about science and its implications. To this end, NIEHS employs citizen-based priority setting through Town Meetings and Brainstorming Sessions held throughout the year in various regions of the U.S. These sessions involve the participation of the senior leadership of the NIEHS, elected officials, local industry, regional offices of other federal agencies, state and county health officials, university scientists, public interest groups, and lay citizens. On average, a Town Meeting attracts an attendance of 200 to 400 participants from the local community.

NIEHS also supports workshops and roundtables under the banner of the National Academy of Sciences to promote awareness and understanding of the new opportunities in environmental health and policy implications of the science. Furthermore, the 40 NIEHS-supported Centers are required to sponsor outreach activities in their local communities.

To ensure that progress is made in translating our science into the practice of medicine, NIEHS has developed several Centers programs that bring basic and clinical researchers (physician scientists) together in the same space. Examples of such programs include our existing Children's Environmental Health Research and Prevention Centers. This year we expect to develop similar centers on Parkinson's disease and breast cancer.

NATIONAL SECURITY

Over the past 35 years, the NIEHS has developed a cadre of first-rate researchers in the environmental health sciences. Five NIEHS-supported Centers in the New York area have more than 100 researchers with expertise in air pollution, asbestos toxicity, exposure assessment, children's health, and population-based epidemiology studies. Since September 11, they have initiated research activities in response to the attack on the World Trade Center with NIEHS support and coordination. Their efforts include exposure assessment, epidemiology, medical care and clinical evaluation, and community outreach and education. These activities are now being integrated into the government-wide effort coordinated by the Federal Emergency Management Agency.

The other area in which NIEHS has expertise and plans to contribute, is in the Nation's preparation to prevent toxicity and death from bioterrorism. Toxicogenomic technologies

discussed earlier are capable of detecting, tracking, and containing chemical poisons or infectious microorganisms. Identification of susceptibility genes and characterization of their function through toxicogenomics can provide importance clues for understanding, and ultimately preventing, the progression of diseases. The specific pattern of gene response can also provide clues about host defense mechanisms which can also be exploited for prevention. NIEHS plans to use the National Toxicology Program to conduct toxicological evaluations of defined mixtures of contaminants identified by environmental monitoring studies of ambient and indoor air and dust; and to evaluate the safety of therapeutic regimens and intervention measures likely to be employed in biological or chemical terrorism events. This technology is not limited to chemicals; it could also identify genes whose expressions are critical for a pathogen to overcome body or host defense mechanisms.

SUMMARY

Investment in environmental health prevention research is the best hope of eliminating the epidemic of disease. Investment in such research will save lives, spare pain and suffering, and save money in the years ahead. The proposed and ongoing research will lead to more effective environmental surveillance systems with the capacity to rapidly analyze and assess the health risks of chemical and biological agents.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Richard J. Hodes
National Institute on Aging

on

Fiscal Year 2003 President's Budget Request
for the National Institute on Aging

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Institute on Aging (NIA) for FY 2003, a sum of $971,709,000, which reflects an increase of $75,645,000 over the comparable Fiscal Year 2002 appropriation. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report, which compared our FY 2001 results to the goals in our FY 2001 performance plan.

Americans over age 65 are more likely today than at any other time in history to be vigorous and productive. Life expectancy, disability rates, and health and wealth indicators have all shown significant improvement over the past decade. At the same time, healthy, comfortable older age continues to elude many Americans, particularly members of certain racial, ethnic, and socioeconomic groups. Diseases of aging, including Alzheimer's disease, cardiovascular disease, osteoporosis, cancer, diabetes, and arthritis, affect too many older men and women, seriously compromising the quality of their lives. And the challenges of dealing with a rapidly aging population will continue to grow: According to data from the U.S. Bureau of the Census, there are today approximately 35 million Americans age 65 and older. If current demographic trends hold, that number will double by the year 2030. NIA is committed to supporting high-quality research to address all aspects of aging, from conditions and diseases that primarily affect older people to physical, behavioral, and cellular characteristics of the aging process.

AMERICANS ARE LIVING LONGER AND HEALTHIER LIVES

Census data indicates that life expectancy in the United States is approximately 76 years, up from about 49 a century ago. This increase is largely due to improvements in health care, nutrition, and overall standard of living for most people. Longevity, particularly "super-longevity" (living 100 years or beyond), also has a significant genetic and molecular component. For example, several genetic polymorphisms are known to confer extreme longevity in animal models, and studies suggest that similar polymorphisms may operate in humans. Scientists have also found that a positive outlook in early life may be associated with greater longevity. More research is needed to understand the connection between early emotional state and length of life.

Not only are Americans living longer, but we're also remaining healthier into old age. The most recent National Long Term Care Survey (NLTCS), the latest of a series of surveys of the U.S. elderly population, continues to document a dramatic decline in the overall prevalence

of physical disability among older Americans over the past two decades. (See Figure 1.) While 26.2 percent of the elderly were assessed as disabled in 1982, this figure dropped to 19.7 percent in 1999. Of particular note is the sharp reduction in disability rates among African Americans during the 1990s, reversing trends from the 80s. Results from the NLTCS also show significant declines in severe cognitive impairment, with 900,000 fewer cases in 1999 than expected based on the 1982 rates – a decline in prevalence from 5.2 to 2.7 percent. The finding that cognitive disability is declining is also supported by evidence from the Health and Retirement Study, which indicated that declines were especially large among those with less than a high school education and those ages 80 and older, groups in whom cognitive impairment is particularly prevalent.

CONQUERING ALZHEIMER'S DISEASE

Alzheimer's disease (AD), the most common cause of dementia among older persons, tragically affects as many as four million Americans, most of whom are 65 or older, according to the Alzheimer's Association. However, we have made progress in several important areas. For example:

We are identifying risk factors. Identifying risk factors for AD will help us identify pathways affecting its development or progression and may lead to better predictors of the disease even before it is clinically apparent. Until last year, just four of the approximately 30,000 genes in the human genome were conclusively known to affect the development of AD pathology. Recent genetic studies suggest that as many as four additional and as yet unidentified genes may also be risk factors for late-onset AD. NIA-supported researchers are attempting to identify other risk factors through population studies.

We are improving our ability to diagnose AD early. Scientists are developing and refining powerful imaging techniques that target anatomical, molecular, and functional processes in the brain. These new techniques hold promise of earlier and more accurate diagnosis of AD, as well as improved identification of people who are at risk of developing the disease. Recent studies suggest that positron emission tomography (PET) scanning of metabolic changes in the brain and magnetic resonance imaging (MRI) scanning of structural brain changes may be useful tools for predicting future decline associated with AD and other neurodegenerative diseases.

We are developing new, more effective treatments for AD. One way to treat AD successfully may be to interfere with early pathological changes in the brain, including the development of AD's characteristic amyloid deposits and neurofibrillary tangles. A number of promising approaches, many of them targeted at the reduction of amyloid plaques, are being developed and tested in various model systems. In 2001, NIA funded research to find new ways to treat AD by targeting underlying disease processes and continuing development of a vaccine to prevent the disease. Recent studies have successfully used antibodies to clear amyloid plaques from the brains of mice that were genetically engineered to develop AD-like pathology. Other recent studies have shown that statins, the most commonly used cholesterol-lowering drug, may be associated with a lower risk of AD (see Figure 2), and that high blood levels of the amino acid homocysteine may increase risk. Increasing intake of folic acid and vitamins B6 and B12 can reduce blood levels of homocysteine, and NIA is planning a clinical trial of these substances to test whether supplementation can slow the rate of cognitive decline in people diagnosed with AD.

NIA is currently supporting 18 AD clinical trials, seven of which are large-scale prevention trials (see Figure 3). These trials are testing agents such as estrogen, anti-inflammatory drugs, and anti-oxidants for their effects on slowing progress of the disease,

delaying AD's onset, or preventing the disease altogether. Other intervention trials are assessing the effects of various compounds on the behavioral symptoms (agitation, aggression, and sleep disorders) of people with AD. The NIA is also supporting studies that are testing interventions for improving AD patient care delivery and alleviating caregiver burden.

UNDERSTANDING THE BIOLOGY OF AGING

We are continuing to advance our understanding of the molecular and cellular changes that underlie aging processes. New technologies are providing answers to questions about how genes control cell and tissue function. Arrays of DNA corresponding to specific genes permit the comparison of expression of tens of thousands of genes at one time to determine which are turned on or off in a particular cell or condition. A collection of 15,000 mouse genes has been developed, including genes active in early development. To facilitate extensive use of this gene collection, NIA has made it available to research institutions worldwide. Verified sequences of each gene in the set are also available; by comparing the sequence information with genes that have already been well studied, scientists may be able to determine the function of these genes in mice. The Institute has also developed the NIA Microarray Facility, which provides investigators with low-cost access to microarrays developed from the set and will also provide for collecting and analyzing the gene expression findings of multiple investigators. Continued discovery of genetic pathways that influence longevity in a variety of experimental animal models may help in identifying both genes and molecular processes that affect health of aging humans.

REDUCING DISEASE AND DISABILITY

In addition to AD, we have made a number of advances in other diseases and conditions. Our knowledge of the beneficial effects of exercise continues to increase; for example, last year researchers found that physical activity can stave off disability in older persons with osteoarthritis of the knee, a form of arthritis that is particularly common among people age 50 and over (see Figure 4). NIA's highly successful campaign to encourage older people to exercise is working to translate research findings into action. Since the campaign was launched in 1998, NIA has distributed over 430,000 copies of its exercise guide and over 55,000 copies of its companion video to the public. In addition, a Spanish-language version of the guide was published in January 2002.

To address disability and disease in special populations, NIA implemented a major new study of health disparities among different racial, ethnic, and socioeconomic groups. The study, Healthy Aging in Nationally Diverse Longitudinal Samples (HANDLS), focuses primarily on cerebrovascular health, cardiovascular health, age-associated changes in cognition, and strength and physical functioning. Through this study, we hope to address hypotheses about aging and health disparities in minority and poor populations to understand the significance of environmental and genetic risk factors for disease. The pilot phase of HANDLS, in which investigators assessed the logistics and feasibility of this community-based study, was completed at the end of 2001, and the larger population-based phase of this study is scheduled to begin in late fall of 2002.

Other important research advances include:

Parkinson's Disease. In an effort to develop a new model of Parkinson's disease, scientists exposed rats to rotenone, a common pesticide. Exposed rats showed pathological changes characteristic of Parkinson's disease, as well as motor behavior abnormalities, such as rigidity and decreased motor activity, that are frequently seen in Parkinson's disease patients.

This new model of Parkinson's disease will be useful in designing and testing new therapeutic interventions, as well as further identifying environmental exposures that may be risk factors for developing the disease.

Diabetes. Diabetes is one of the major debilitating diseases that affect older people. Among the elderly, type 2 diabetes is the most common; it occurs when pancreatic beta cells produce insufficient insulin or when the body cannot use its insulin efficiently. NIA-supported researchers participated in the Diabetes Prevention Program, a major, 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. (See Figure 5.) 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. Nearly half of the study participants were members of racial and ethnic groups that suffer disproportionately from type 2 diabetes, including African Americans, Hispanic Americans, Asian Americans and Pacific Islanders, and American Indians.

Cancer. Much remains unknown about cancer diagnosis, prevention, and treatment in older people. NIA supports a variety of cancer-related basic and clinical research projects, many of them in collaboration with the National Cancer Institute (NCI) and other NIH Institutes. For example, NIA has an initiative to expand knowledge on aging- and age-related aspects of prostate cancer in different populations. NIA and NCI have also created a partnership that has resulted in an aggressive research agenda within the NCI-designated cancer centers to reduce the burden of cancer for older persons.

Hip Fracture Recovery. According to a recent study (Marcantonio et al., J Am Geriatr Soc 48: 618-624, 2000), 250,000 older Americans fracture a hip each year, and delirium, an acute confusional state, complicates recovery from hip fracture repair in at least one-third of these people. Besides being frightening to patients and their families, and difficult to manage in the hospital, delirium after hip fracture is also associated with poor recovery of function in both the short and long term. In a recent study aimed at reducing risk factors for delirium, geriatricians provided a variety of recommendations to the orthopedic physicians caring for the hip-fracture patients. This intervention led to a one-third reduction in the number of patients who developed delirium and a one-half reduction in the patients who developed severe delirium.

Estrogen Replacement Therapy. Each year, millions of American women turn to hormone replacement therapy (HRT) to relieve peri- and post-menopausal symptoms and for protection against age-related conditions such as heart disease and osteoporosis. However, HRT can have unwanted side effects. In a recent clinical trial, women over age 65 received one of three doses of estrogen. The highest dose was the amount most commonly prescribed today, and the lowest dose was one-fourth of this amount. They found that the low dose markedly reduced bone breakdown, a reduction that was similar to that produced by the highest dose, and reduced the frequency of common side effects. In fact, low-dose therapy resulted in no more side effects than placebo. These findings suggest that a lower dose of estrogen may be just as effective as the regular dose, but have fewer side effects.

Cardiovascular Disease. An exciting area of stem cell research lies in the ability of the body to use its own stem cells to repair damaged organs. In a recent study, mice with induced heart damage were injected with particular proteins called cytokines. Stimulated by the

cytokines, the mice's own primitive bone marrow cells migrated to the heart, converted to several different types of cardiac cells, and contributed to repair of the damaged tissue, improving both heart function and survival of the treated mice. (See Figure 6.) In a study of human heart transplant patients, scientists found that primitive cells from heart transplant recipients can migrate to and become a functioning part of the donated heart. These results are extremely preliminary, and further research is needed. However, the findings from these studies challenge the conventional wisdom that damaged heart tissue cannot be regenerated, and suggest that the body's own naturally-occurring stem cells may be able to repair tissue damage and fight disease.

CONCLUSION

It is becoming increasingly obvious that old age need not be associated with illness, frailty, or disability. In fact, we have made tremendous progress against all of the major diseases and conditions of aging. However, much work remains to be done. By continuing and intensifying research, NIA can move forward in meeting the promise of extended life by improving the health and well-being of older people in America.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Stephen I. Katz
National Institute of Arthritis and Musculoskeletal and Skin Diseases

on

Fiscal Year 2003 President's Budget Request
for the National Institutes of Arthritis and Musculoskeletal and Skin Diseases

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases for FY 2003, a sum of $488,228,000, which reflects an increase of $37,988,000 over the comparable Fiscal Year 2002 appropriation.

It is an honor for me to have this opportunity to share stories of research advances as well as highlights of the many opportunities we have in research on bones, muscles, joints, and skin. The mission areas of our Institute touch the daily life of millions of Americans, and we are committed to improving quality of life as well as longevity. Diseases within our mandate know no barriers in terms of age, gender, ethnicity, or socioeconomic status. In fact, many of the diseases in our mission areas disproportionately affect women and minority individuals, and we are committed to determining why this is the case.

RESEARCH IN CHILDREN

While we typically associate chronic diseases with the elderly, the fact is that they can affect people of all ages, and can rob a child of the joys and activities of the young. The other reality is that children are not small adults – diseases affect them in different ways and treatments may have different effects in children than adults. In light of these and other realities, the NIAMS has undertaken a number of programs and activities focused on children to enhance our understanding of childhood diseases and to develop improved treatments for our younger generation. For example, it has been said that osteoporosis is actually a disease of childhood that is manifested in later years. We know how vitally important it is that children develop a strong skeleton in childhood so that they can withstand the age-related changes that occur in their bones later in life. Research supported by the NIAMS has resulted in the design of a 7-month, high intensity jumping regimen that will increase peak bone mass at two clinically

critical sites, the hip and the spine. Investigators discovered that children who participated in the jumping program had a significantly greater change in bone mineral content in both the hip and spine compared with a control group, as well as showing positive differences in bone mineral density and bone area. This regimen, which can easily be incorporated into the regular elementary school curriculum, has potentially important public health implications with respect to optimizing peak bone mass attainment in young people.

The NIAMS has also placed an enhanced emphasis on research on osteogenesis imperfecta (OI), one of the most common genetic diseases of bone. OI is characterized by brittle bones that fracture easily, and is caused by mutations in the gene for a protein called type I collagen. NIAMS-supported researchers have recently reported very exciting progress in both the controlled introduction of genes into bone cells, as well as the ability to inactivate mutant genes that can cause disease. Further progress in OI research is expected as a result of several new grant awards from the NIAMS for projects ranging from cutting-edge gene and cell therapies to testing drug treatments in mouse models of the disease.

In other research related to children, the NIAMS continues to lead the NIH's Pediatric Rheumatology Clinic. In addition to providing diagnosis, evaluation, and treatment of juvenile arthritis and other rheumatic diseases, the clinic facilitates the translation of research advances to improve patient care. A new study underway at the clinic is designed to determine the best medication combinations for treating children with juvenile rheumatoid arthritis. We recognize that we have much to learn about diseases in children and we are currently developing a new, broad initiative that will focus on multidisciplinary translational research projects in rheumatic and immuno-inflammatory skin and muscle diseases of children so that we can target those areas that present special challenges in children.

ARTHRITIS AND OTHER RHEUMATIC DISEASES

Research on osteoarthritis, a degenerative joint disease, took a big step forward with the launching of the new public-private partnership that teams several NIH entities, the FDA, and four pharmaceutical companies in the Osteoarthritis Initiative. Clinical research on osteoarthritis has been severely hampered by the lack of biological markers needed to assess the progression of this most common form of arthritis. The significant commitment required to undertake such a study has been beyond the scope of either government or industry alone, but is feasible and indeed underway through this new partnership. The NIAMS teamed with our colleagues in the National Institute on Aging in leading this effort to fund from four to six clinical research centers to establish and maintain a natural history database for osteoarthritis. The database will include clinical evaluation data and radiological images, as well as a biospecimen repository. All data and images collected will be available to qualified researchers worldwide to

help hasten the pace of scientific studies and biomarker identification. In a separate effort, the NIAMS is supporting work to develop biomarkers for two chronic inflammatory diseases which affect many Americans, rheumatoid arthritis and lupus.

Lupus is a serious and potentially fatal autoimmune disease that occurs with greater frequency and intensity in African American women, and it affects many organ systems of the body. One of the challenging manifestations of lupus is the involvement of the nervous system, and researchers supported by the NIAMS have recently reported significant advances in our understanding of the molecular mechanisms involved in the changes that can occur in the brains of people with lupus. The identification of the particular antibodies involved not only helps us to understand the nervous system complications in lupus, but also provides some new therapeutic possibilities for this aspect of lupus that can be difficult and challenging for affected patients, their families, and their health care providers. To further enhance research in this area, the Institute has recently released a solicitation for applications on neuropsychiatric lupus, in an effort to stimulate additional study of the neurological and psychiatric syndromes associated with this chronic disease.

BONE BIOLOGY AND BONE DISEASES

Basic researchers have reported new insights into the complex effects of estrogen on bone. We know that the most common cause of bone loss is the decline in the female sex hormone, estrogen, in women after menopause. Estrogen also appears to be important in maintaining bone mass in men, although men have more of the male sex hormone androgen than estrogen. Recent research reports from work supported by the NIAMS have provided important clues to the complex relationship between estrogen and bone, and revealed–as many research investigations do–that we still have much to learn about the action of estrogen as well as the function of estrogen receptors. The most recent research reports indicate that either estrogen or androgen can act to increase bone formation and prevent net bone loss. In other research, scientists have shown that particular cells of the immune system called T cells can contribute to the bone loss that occurs when estrogen levels are low. These and other basic studies funded by the NIAMS are adding to the foundation of knowledge of normal function in bone biology and the changes that occur in bone diseases. Recent initiatives to stimulate further work in the bone sciences include the release of solicitations to encourage applications on new research strategies for the evaluation and assessment of bone quality, and one on basic and applied stem cell research for arthritis and musculoskeletal diseases.

MUSCLE BIOLOGY AND MUSCLE DISEASES

This has been a very active year in the whole field of the muscular dystrophies as the NIAMS has joined our colleagues in the NINDS in targeting research in this area.

Over the last two years, we have supported two successful scientific conferences, and issued research solicitations to the research community targeting those areas of particular opportunity that were identified by experts at the conferences. As a result of these activities, the NIAMS and NINDS recently awarded several new grants to support both basic and clinical research studies in facioscapulohumeral dystrophy (FSHD), the third most common genetic disease of skeletal muscle. We have also funded a number of projects in follow-up to a solicitation for proposals on therapeutic and pathogenic approaches for the muscular dystrophies. In addition, we continue to support a research registry in particular forms of muscular dystrophy that serves as an invaluable resource for scientists to collect and analyze new research data in their pursuit of better treatments for muscular dystrophies.

SKIN BIOLOGY AND SKIN DISEASES

Chronic wounds are a significant public health challenge, particularly in the elderly and people with diseases like diabetes that affect skin healing. A new living skin substitute showed a significant improvement in wound healing and a decrease in time to complete closure of the wound in people with diabetic foot ulcers. Newer technologies such as artificial skin equivalent systems can improve the rate of healing of existing wounds, as well as minimize or reduce the incidence of severe complications.

Pseudoxanthoma Elasticum (PXE) is a systemic inherited disorder that affects the elastic tissue in the skin, eyes, and cardiovascular system, and it can result in severe and even fatal problems in affected individuals. The fascinating new dimension to our understanding of PXE is that, contrary to earlier beliefs, PXE is actually a metabolic disorder. The recognition that this is a metabolic disease offers new hope for the development of treatments based on metabolic modifications potentially including such approaches as diet manipulation or drug therapy. There is also the potential for PXE to be identified in affected people early so that treatment can be instituted before signs and symptoms of the disease actually occur. To boost research on PXE and other heritable disorders of connective tissue, such as Marfan syndrome and Ehlers-Danlos syndrome, the Institute recently released a solicitation, along with our colleagues at the National Heart, Lung, and Blood Institute, to encourage more basic and clinical studies of these disorders.

HEALTH DISPARITIES

A number of diseases within the mission areas of the NIAMS affect women and members of minority groups disproportionately, including lupus, scleroderma, osteoarthritis, vitiligo, and keloids. In addition to the vigorous research portfolio that the NIAMS funds in these areas, I want to cite two programs that the Institute supports that address the critically important area of health disparities. We continue our active involvement in the Health Partnership Program, a model community-based research

program to study rheumatic diseases in the African American and Hispanic/Latino communities in the metropolitan, Washington, D.C., area. In addition, we enthusiastically support a newly initiated program that the NIAMS was active in creating – a new strategy for enhancing clinical research training in minority-serving institutions. The goal of this program is to produce well-trained clinical researchers who will go on to lead clinical research projects. Finally, in follow-up to a major scientific conference organized by the Institute, the NIAMS is developing a new initiative on health disparities in rheumatic and skin diseases.

INTRAMURAL RESEARCH PROGRAM

The NIAMS Intramural Research Program (IRP) is a vital and growing program that has become a national and international resource, as well as a recognized site for scientific excellence on the NIH campus. A major new program that the IRP has undertaken is the initiation of a trans-NIH collaboration in musculoskeletal medicine. This effort will include the development of innovative fundamental science, clinical studies, and translational research. The collaboration is designed to build on strengths that are already present at the NIH, as well as foster the growth of new research and training programs in the critical and under-served area of musculoskeletal medicine.

CONCLUSION

Virtually every home in America is touched by diseases affecting bones, joints, muscles, and skin. We are committed to better understanding, diagnosis, treatment, and prevention of these diseases and disorders that are typically chronic, costly, common, and disabling. The vitality of our bones, joints, muscles, and skin is key to the length and quality of our lives. Medical research supported by the NIAMS has made significant strides in improving health and quality of life, and we are committed to pursuing promising research opportunities that will continue to improve the health of the American people.

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is the NIH's second annual performance report which compared our FY 2001 results to the goals in our FY 2001 performance plan.

I will be happy to answer any questions that you may have.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. James F. Battey, Jr.
Director, National Institute on Deafness and Other Communication Disorders

on

FY 2003 President's Budget Request
for the National Institute on Deafness and Other Communication Disorders

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) for FY 2003, a sum of $371,951,000, which reflects an increase of $28,880,000 over the comparable FY 2002 appropriation. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compared our FY 2001 results to the goals in our FY 2001 performance plan.

Disorders of hearing, balance, smell, taste, voice, speech, and language exact a significant economic, social, and personal cost for many individuals. The NIDCD supports and conducts research and research training in the normal processes and the disorders of human communication that affect many millions of Americans. Human communication research now has more potential for productive exploration than at any time in history. With substantive investigations conducted over the past decades and the advent of exciting new research tools, the NIDCD is pursuing a more complete understanding of the scientific mechanisms underlying normal communication and the etiology of human communication disorders. Results of this research investment will foster the development of more precise diagnostic techniques, novel intervention and prevention strategies, and more effective treatment methods.

Excessive noise has long been recognized as an occupational hazard among adults, and hearing conservation programs have been implemented in the workplace. However, the resiliency of a child's auditory system following noise exposure needs further research. Chronic exposure to loud music, fireworks, lawn mowers or toys can accumulate over a lifetime to gradually produce irreversible damage to the sensory cells of the inner ear. The results of a recent survey conducted by the Centers for Disease Control and Prevention revealed that approximately 5.2 million American youths have some degree of hearing loss due to exposure to noise at hazardous levels.

Identification of Genes Causing Deafness. Hearing loss occurs with a frequency of about 1 in 1,000 newborns and is also a prevalent, but not necessarily inevitable, feature

of the aging process. Causes of hearing loss in children and the elderly include viral and bacterial infections, loud noise, head trauma, drugs or other chemicals that are toxic to the sensory cells of the inner ear, as well as mutations in genes critical for normal auditory function and development. NIDCD scientists are identifying the genes whose mutations result in hearing loss. Recently, NIDCD Intramural scientists identified a gene located on chromosome 10 that is involved in Usher syndrome type 1D (USH1D). Individuals that inherit two copies of this mutated gene are born profoundly deaf, have severe balance problems and gradually lose their sight beginning in adolescence. The scientists discovered that USH1D gene encodes a protein called cadherin-23. Knowledge of the function of cadherin-23 in the inner ear will provide new insight into cellular processes essential for normal auditory function, which may ultimately guide the development of improved diagnosis and treatment methods. NIDCD expects to support collaborations between its Intramural scientists and those of the National Eye Institute in these areas.

NIDCD scientists also identified a gene (DFNB29) located on chromosome 21 whose mutation caused recessively inherited hearing loss. This gene encodes a protein, claudin-14, which is believed to help seal adjacent cells together in the inner ear thus preventing the leakage of endolymph fluid. The endolymph bathes the sound transduction cells and is essential for conversion of the mechanical energy of sound into an electrical signal that is sent to the brain. Studies are underway in a new mouse model to advance our understanding of the function of claudin-14.

Discovery of Novel Deafness Genes and Genetic Characterization of Hearing Impairment. NIDCD has developed a substantial research portfolio to study existing mouse mutants as well as creating new mouse models to facilitate the discovery and analysis of genes whose mutation causes hereditary hearing impairment in humans. In a recent study utilizing the mouse mutant Waltzer, NIDCD Intramural scientists showed that mutations in the human cadherin gene family cause Usher Syndrome type 1D. This mouse model is a critical research tool for determining the identification of the mechanisms by which cadherin mutations cause this devastating deafness and blindness syndrome. In another NIDCD-supported study, a mouse nuclear gene has now been shown to interact with mutated genes in the mitochondria to significantly alter the severity of age-related hearing loss. This model system should provide important information regarding age-related hearing loss in humans, a relatively common and debilitating health problem within the aging U.S. population. These findings underscore the power of mouse genetics and the value of mouse models of deafness for the identification and detailed molecular characterization of human hearing impairment.

Scientists Identify Sweet Taste Receptor Gene. Understanding the molecular and cellular events that occur at the early stages of taste perception at the level of the taste receptor cell provides important insight into how we taste different sweet, bitter, salty and sour substances. A variety of distinct signaling pathways are activated by the basic

taste qualities of salty, sour (acid taste), sweet, and bitter. Salty- and sour-tasting compounds activate ion channels that are located at taste receptor cells clustered within taste buds of the tongue and palate while bitter and sweet compounds bind to G protein-coupled receptors. Recently, four NIDCD-supported laboratories independently identified a gene, T1R3, at the mouse *Sac* locus that encodes a sweet taste receptor subunit. Differences in sweetener intake among inbred strains of mice are partially determined by variation in genes at the saccharin preference (*Sac*) locus. It was determined that the T1R3 receptor differs in amino acid sequence in "sweet preferring" versus "sweet indifferent" mouse strains. Both human and mouse T1R3 are G protein-coupled receptors, and are selectively expressed in subsets of taste receptor cells that are sensitive to sweet substances.

Abilities in Auditory Pitch Recognition are Largely Inherited. Auditory pitch recognition is a complex process that allows us to determine the pitch or tone of a sound. In this process, the ears receive the sound signal and the brain interprets this signal to produce the pitch we perceive. Individuals with problems in pitch recognition are sometimes referred to as "tone deaf." Severe deficits in pitch recognition may be associated with speech and language disorders. It was long known that tone deafness can run in families. However, it was not known whether this disorder was due to inherited genes or to a common environment shared by family members. To answer this question, NIDCD Intramural scientists performed a large study on twins. The results show that identical twins scored much more alike than fraternal twins on a Distorted Tunes Test. The data revealed that approximately 70-80% of an individual's score is due to their genes and 20-30% due to other factors. The discovery that individual differences in pitch recognition are mostly genetic opens up the possibility of using genetic methods and information from the Human Genome Project to find the genes essential for pitch recognition. Identifying such genes and how they function will provide new insight into how the brain processes sound.

How Basic Biology Translates into New Technology to Help the Hearing Impaired. Over the past decade, NIDCD-supported scientists have been studying the amazing auditory capability of *Ormia ochracea*, a tiny parasitic fly with such acute directional hearing that it has inspired a new generation of hearing aids and nanoscale listening devices. *Ormia* can detect very small differences in sound-source position, a situation analogous to humans trying to detect who is speaking in a crowded room. This accomplishment is due to the unique anatomy of the eardrums of *Ormia*. The fly's eardrums are connected internally by a cuticle-based bridge that functions as a flexible lever. This unusual structure allows the membranes of the eardrum to vibrate in response to sound in two distinct ways, with different resonant frequencies. Trying to mimic the *Ormia* ear in silicon, engineering groups so far have developed prototype "microphone eardrums" that function "*Ormia* -like" as predicted but at ultrasonic frequencies. Additional research will be needed to generate prototypes that detect sound in the range of normal human hearing, that will be highly directional, fit inside the ear

canal, and be affordable. Other applications of the *Ormia*-inspired silicon ear might include robotic listening devices. These latest findings have led to collaborations between neurobiologists and engineers to make a directional hearing aid that would be smaller, simpler and cost less than currently available devices.

Although hearing aid technology has advance rapidly over the last few decades, the various hearing aids available still do not function well in real world situations where sound from more than one source is present, and they are not particularly effective in restoring the listener's ability to cope with the problem of attending to a single speech source among competing speech sources. NIDCD-supported scientists are actively engaged in research to develop "intelligent" hearing aid systems that are capable of selectively locating and characterizing a sound in a crowd.

Functional Brain Imaging as a Tool to Understand Cochlear Implant Performance. The cochlear implant is the first clinically useful neural sensory prosthesis to replace a human sense. It converts sound into electrical impulses on an array of electrodes that is surgically inserted into the inner ear, bypassing the inner ear hair cells and stimulating the auditory nerve directly, restoring the perception of sound to persons who are totally, or almost totally, deaf. This device has allowed adults who lost their hearing to recover an ability to understand speech. Although speech perception performance of adults has steadily increased with new advances in cochlear implantation, wide performance variations exist among cochlear implant recipients. Differences in structural and functional abnormalities of the auditory system may play a role in this variability. However, little is known about the reorganization of the auditory system following deafness, or on the preservation or recovery of auditory function following cochlear implantation. NIDCD-supported scientists have completed preliminary studies examining functional brain imaging in individuals before and after cochlear implantation. The data suggest that preoperative to postoperative changes in the brain's responsiveness as measured by imaging are related to improvements in speech perception scores. Also, despite relatively similar hearing losses in each ear, significant differences in preoperative auditory cortex activation were observed between ears, which may help guide selection of the more appropriate ear for implantation.

Phase I Clinical Trial of an Otitis Media Vaccine Candidate. Otitis media (OM) is the most common reason for a sick child to be evaluated by a physician, a public health burden estimated to cost approximately $5 billion a year in the U.S. In addition to the cost savings, prevention of OM is particularly important because repeated antibiotic treatment of OM often results in the appearance of drug-resistant strains of bacteria which can no longer be eradicated with first-line antibiotics. NIDCD Intramural scientists have developed candidate vaccines that would protect infants from OM caused by two major bacterial pathogens: nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis*. These two pathogens account for two-thirds of OM cases in children, and there is no vaccine available for prevention of the disease. Pre-clinical testing with such

vaccines from nontypeable *H. influenzae* demonstrated that the vaccines could generate specific immunity against the bacteria and reduce bacterial colonization in nose and throat, and reduce the incidence of OM in animal models. Additional clinical trial involving 40 normal human adult volunteers, one such vaccine directed against *H. influenzae* proved to be both safe and effective, eliciting a significant immune response against the bacteria. This candidate vaccine will soon be tested in a second trial for safety and effectiveness in children. For *Moraxella catarrhalis*, similar preclinical approaches were taken, resulting in several candidate vaccines. Pre-clinical testing in animal models with vaccines for *Moraxella catarrhalis* demonstrated that the vaccines were safe and effective, eliciting a significant immune response that inhibited bacterial growth.

Additional clinical trials are planned to test these candidate vaccines for safety and efficacy in humans.

Genetic Testing and the Clinical Management of Nonsyndromic Hereditary Hearing Impairment. In the last decade, approximately 20 genes whose mutations result in nonsyndromic hearing impairment have been identified and isolated. Mutations in one of these genes, GJB2, accounts for about 25% of all autosomal recessive nonsyndromic hereditary hearing impairment in American children. With the identification of genes that contribute to hearing function, genetic testing becomes technically possible but not necessarily suitable for widespread clinical application at present. With the enactment of some type of legislation that requires universal hearing screening for newborns in 36 states, not only are infants with severe hearing impairment identified much earlier in life but infants with lesser degrees of hearing impairment are now also being identified. Many unresolved issues remain for clinicians as they characterize auditory performance in a newborn who fails hearing screening, design intervention strategies to optimize communicative success and ensure that a "medical home" exists for the infant with hearing impairment. The advances in the genetics of hereditary hearing impairment and in the early identification of hearing impairment have now converged. These advances have led some to suggest genetic testing/evaluation for all infants who are identified with a hearing loss at birth. In consideration of these developments, the NIDCD and the National Human Genome Research Institute are collaborating on an initiative to address the clinical relationship between genetic and audiologic/otologic information, as well as to address the clinical validity and utility of genetic testing in the diagnosis, treatment and management of nonsyndromic hereditary hearing impairment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Richard K. Nakamura, Acting Director
National Institute of Mental Health

on

Fiscal Year 2003 President's Budget Request
for the National Institute of Mental Health

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 FY 2003, a sum of $1,359,008,000, which reflects an increase of $105,358,000 over the comparable Fiscal Year 2002 appropriation.

In my statement I will highlight new NIMH initiatives that represent both what we are doing proactively to better meet the clinical treatment needs of people with severe mental disorders, and how we are responding to urgent national needs, including the psychological aftermath of the September 11 terrorist attacks. I also will describe selected findings that illustrate how NIMH is exploiting advances across a broad spectrum of neuroscience and behavioral science toward our goal of understanding the brain – and, of understanding how, when its processes go awry, mental disorders can occur.

MENTAL ILLNESS IS REAL AND CAN BE TREATED EFFECTIVELY

From our perspective at NIMH, one of the signal accomplishments of the past decade has been the continuing destigmatization of mental illness. Many parties, from patients and families, to grass roots organizations, to the media, to government have contributed to the task of public education. The landmark *Surgeon General's Report on Mental Health* struck a resounding chord with millions of Americans. Supported by a meticulous review of current scientific knowledge, it issued a straightforward message: Mental illnesses are real and are treatable, and recovery is possible. More than a scientific communication, this is a message of hope that has raised spirits across our Nation. As a marker of the success of NIMH in continuing to disseminate accurate education about mental disorders, I would note that our award-winning home page (www.nimh.nih.gov) now registers some 7 million hits each month.

DEVELOPING NEW TREATMENTS FOR MENTAL ILLNESSES

Of course, our educational efforts must be backed up by productive science. We are confident our investments in basic science are on the right track. We also have launched an unprecedented series of clinical effectiveness trials characterized by large sample sizes and relatively few exclusion criteria; in order to further ensure the generalizability of findings, these trials occur not only in academic clinics but also in more "real world" settings including primary care settings. We are assessing outcome on the basis of symptom reduction and also use measures of functional rehabilitation. The approach also calls for aggressive dissemination of results.

Now, in a major new enhancement of treatment improvement research, NIMH is launching a sweeping initiative designed to introduce fundamentally new approaches to the development of treatments for mental disorders. Somatic and psychological treatments available today are highly effective for many people with mental disorders. For significant numbers of persons, however, extant treatments are not effective. Too much time may be required for medications to exert therapeutic effect, thus rendering a treatment impractical in some instances; in other cases, certain individuals do not respond sufficiently to achieve full remission from an acute episode of illness or to avoid recurring episodes. With the advice of the Treatment Development Workgroup of the National Advisory Mental Health Council (NAMHC), we are exploring how federally funded research complements and can leverage work being conducted in the private sector. With respect to medications development, for example, we plan to step up our efforts to generate information needed by private sector entities whose business it is to develop and test promising new compounds. Additionally, a challenge of immediate importance for NIMH is to encourage the field to move beyond thinking of new treatments only from the perspective of diagnostic entities such as schizophrenia or depression, and to focus down to the component symptoms that combine to form global diagnostic entities. Schizophrenia, for example, is characterized by dimensions such as disorganized thinking, misperception of reality, and cognitive impairment. The Food and Drug Administration (FDA) currently approves most drugs for psychiatric disorders only for diagnoses categorically defined in the Diagnostic and Statistical Manual (DSM) of Mental Disorders (4^{th} Edition). Research that leads to an appreciation of psychiatric diagnoses as "multi-dimensional" will position NIMH to partner with FDA and industry to achieve consensus on appropriate methods and clinical endpoints other than DSM diagnoses. If symptom complexes such as cognitive impairment in schizophrenia were to be recognized by the FDA as legitimate targets for new drug registration, the pharmaceutical industry would be provided with powerful incentives to develop treatments targeting these specific disabilities and great benefits in health might accrue.

The Treatment Development Initiative will be an Institute-wide enterprise, with a key role to be assumed by the intramural Mood and Anxiety Disorders Program. This

newly established program has recruited senior investigators from academia and now stands at the leading edge of research aimed at understanding and measuring structural changes in the brain associated with depression, chronic stress, and post-traumatic stress disorder, and at developing brain-based biomarkers to be used in monitoring treatment progress and outcome. Other research objectives will encompass studies of gene expression of proteins that may serve as potential targets for new drugs, development of more informative animal models, preclinical development of promising new compounds, and efforts to better dissect DSM syndromes into component dimensions that can be targeted for specific treatment.

Meeting the urgent goal of expanding the array of interventions that will be effective for more individuals with disorders is contingent on our long-term investments in diverse areas of research. I would like to highlight a few findings reported by NIMH-funded investigators over the past year indicating that we are, indeed, realizing dividends from our research conducted over the course of many years, for example, in refining brain imaging technologies and in exploiting cutting edge tools such as molecular genetics in the study of mental disorders.

VISUALIZING BRAIN CHANGES IN CHILDHOOD SCHIZOPHRENIA

Schizophrenia, the subject of the acclaimed new film, *A Beautiful Mind*, based on the book by Sylvia Nassar, is a cruel disease. According to the World Health Organization, schizophrenia affects approximately 1 percent of the population globally. The illness most often manifests in late adolescence or early adulthood. Psychotic symptoms, including hallucinations and delusions, can be severely and persistently disabling. Understanding brain changes that correlate with psychotic symptoms will give us insight into the origins of schizophrenia. In recent years, imaging studies have shown changes in the volume of various brain structures that correlate with a diagnosis of schizophrenia. Last year, a team of NIMH investigators reported a study that used magnetic resonance imaging (MRI) to examine, over the course of 5 years, a group of teenagers with relatively rare early-onset schizophrenia, and to compare the brain scans of these young patients to those of a group of healthy controls. In the ill children, gray matter loss began in a small region of the parietal cortex, where gray matter is lost normally in adolescence. Over the course of the study, however, the images revealed a virtual wildfire of tissue loss spreading across the brains of these teens as schizophrenia progressed; the extent of these structural changes reflected the severity and time-course of symptoms. Identifying these changes and their causes will help researchers to understand the mechanisms of psychotic disorders and, in the long run, develop better treatments.

SEEKING CLUES TO GENETIC VULNERABILITY FOR AUTISM

Although no specific genes have been identified to date and no specific region of the genome has been linked unambiguously to autism, the presence of a strong genetic component is incontrovertible. The genetic, or heritable, component is thought to account for as much as 90 percent of the liability for autism. Evidence to date is most consistent with involvement of multiple genes, each having small effect, that together with nongenetic factors produce vulnerability. A number of Institutes are collaborating on studies of autism, and the pace of research is encouraging. Last year, an NIMH grantee reported a potential linkage to autism of variants of a gene called *wnt2*. The gene is expressed in the brain's thalamus, a region important for integrating information. The product of the *wnt2* gene appears to play a key role in brain development and behavior. The finding is intriguing in light of other studies demonstrating that mice that lack a signaling molecule called "Disheveled," which is in the same molecular pathway as *wnt2*, exhibit reductions in general social interactions, in huddling during sleep, and in other grooming behaviors – all behaviors that suggest symptoms of autism The promise of genetics research is to shed light on the biology of the illness and, in turn, to lead to earlier diagnosis and improved treatments; ultimately, of course, we anticipate that genetics studies will lead to preventive interventions.

As this basic work proceeds, I wish to note that NIMH maintains a network of Research Units on Pediatric Psychopharmacology, or RUPPS, that includes five research groups dedicated to evaluating treatments for autism, examining, for example, dose ranges and regimens of medications and their effects on cognition, behavior, and development. Complementary studies of pediatric pharmacology are being supported by the National Institute of Child Health and Human Development (NICHD). I also am pleased to report that NIMH and NICHD soon will launch the first round of funding in the new STAART (Studies to Advance Autism Research and Treatment) Centers program called for in the Children's Health Act of 2000.

9/11: RESPONDING TO THE PSYCHOLOGICAL AFTERMATH

In opening, I mentioned that the Institute has been involved in our national response to the September attacks on our Nation. Even as we mourn the loss of the more than 3,300 persons who lost their lives that day in New York, Washington, and Pennsylvania, we must attend also to the cost of those tragic events to millions of Americans who have suffered and are living with horrific images and memories of 9/11. While communities are pressed to deal with immediate problems, it is important to learn what we can from these terrible events. NIMH is utilizing multiple research mechanisms, including Rapid Assessment Post Impact of Disaster (RAPID) grants and supplements to existing longitudinal and clinical studies. The RAPID program was established years ago to support research in the aftermath of an unforeseen event that necessarily requires expedited peer review and funding consideration. From a large

number of inquires, we invited approximately 18 applications to undergo peer review. These propose to address topics including the epidemiology of exposure and reactions; the nature of settings in which victims/survivors present for care and what types of care are provided; the mental health impact of bioterrorism and on-going threats; the mechanisms by which trauma confers risk for adverse health outcomes; and use of various interventions to reduce the risk of disorder and disability. Several projects now are in review and plans are being made for funding.

In addition, we are enhancing ongoing epidemiological and clinical research studies by adding questions relevant to the impact of the attacks. For example, questions related to exposure to terrorist attack and the subsequent psychological distress were added to ongoing studies o f adult and child mental health being conducted by investigators in New York. Research on the neurobiological mechanisms by which trauma increases the risk of mental disorder for children and adults also is being conducted in New York, and now will involve victims/survivors of the World Trade Center attacks. NIMH will also be looking to a number of national surveys of health and mental health to provide estimates of prevalence of mental disorders, functional impairments and disability, services needed and being used before and after the attacks.

In this context, we know that post-traumatic stress disorder, or PTSD, can be a chronic, debilitating disorder that develops in some but not all people exposed to severely threatening trauma. Insomnia and non-restorative sleep – and nightmares representing the trauma – are recognized symptoms of PTSD. Recent research indicates a relationship of dream characteristics and early adaptive vs maladaptive patterns of processing traumatic memory. These findings have immediate clinical utility in helping suggest persons to whom early treatments should be targeted.

JOHN EDWARD PORTER NEUROSCIENCE RESEARCH CENTER (NRC)

We are pleased that work is progressing on schedule in construction of the NRC. The foundation is being poured imminently, and six NIH institutes that have programs in neuroscience are slated to begin working in the facility in January 2004. Ultimately, the neuroscience programs of ten Institutes will be housed in the Center, greatly facilitating the exchange of information and its translations into clinical applications.

NIMH DIRECTORSHIP

Dr. Steven E. Hyman, NIMH Director from 1996 to December 2001, has returned to Harvard University as Provost. While we miss his energy and vision, we plan to continue build on the progress of the past five years. A national search for a permanent director is underway.

Mr. Chairman, the NIH budget request includes performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report, which compared our FY 2001 results to the goals in our FY 2001 performance plan. I will be pleased to respond to any questions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Glen R. Hanson, Acting Director
National Institute on Drug Abuse

on

Fiscal Year 2003 President's Budget Request
for the National Institute on Drug Abuse

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Institute on Drug Abuse for FY 2003, a sum of $967, 898,000 which reflects an increase of $76, 960,000 over the comparable Fiscal Year 2002 appropriation.

NIDA'S STRONG RESEARCH FOUNDATION

I feel very honored to be serving as the Acting Director of the National Institute on Drug Abuse (NIDA) at a time when new discoveries of significant promise are transforming our understanding of the brain and body and providing us with the knowledge we need to confront both the new and the old realities of the day.

Budget increases, visionary predecessors, and the unprecedented pace in neurobiology have allowed the National Institute on Drug Abuse to establish a strong research foundation from which to alleviate the complex public health problem of drug abuse and addiction. As the world's leading supporter of research on the health aspects of all drugs of abuse, including nicotine, NIDA addresses the most fundamental and essential questions about drug abuse and addiction, which range from understanding how drugs act on the brain; to identifying and minimizing the role that stress can play in drug use and relapse; to detecting and responding to emerging drug use trends such as "Ecstasy" and prescription drugs." This portfolio also continues to elucidate our understanding of drug abuse as a preventable behavior and drug addiction as a treatable disease.

Coupled with strong research is our ability to expand its dissemination to clinicians. Through coordinated dissemination and translational research efforts, NIDA ensures that even the most basic neurobiology discoveries systematically influence community prevention and treatment providers across the country so that our citizens can live healthier and more productive lives. For example, almost 1000 people from both rural and urban communities are participating in treatment protocols where they are receiving science-based drug addiction treatment and medical care through their

participation in NIDA's National Drug Abuse Treatment Clinical Trials Network (CTN). And even more citizens are stopping the initial use of drugs by participating in prevention programs that follow the science-based prevention principles identified and disseminated by NIDA. Much has been accomplished, but more remains to be done.

DRUG ABUSE IS COSTLY AT MANY LEVELS

Directly or indirectly, every family and community is affected by drug abuse and addiction. We all have family members, friends, or acquaintances who abuse some substances. These drugs take a tremendous toll on our society; and they are costly at many levels. At the economic level, the cost of illegal drugs to our Nation was estimated by the White House Office of National Drug Control Strategy to be more than $161 billion in 2000. When one adds the cost of the Nation's deadliest addiction – use of tobacco products – the cost soars to nearly $300 billion each year.

Drug abuse is inextricably linked with the spread of infectious diseases such as HIV/AIDS, tuberculosis, and hepatitis C, and is also associated with domestic violence, child abuse, and other violent behavior. But because our research has shown that drug abuse is preventable and drug addiction is treatable, there is much reason for optimism.

BRINGING A MULTI-DISCIPLINARY APPROACH TO DRUG ABUSE PREVENTION RESEARCH EFFORTS

Researchers have learned much about why people use drugs and have identified many of the risk and protective factors that can influence drug use. In the past year, research has also revealed new insight into how to tailor anti-drug messages to sensation-seeking adolescents to actually reduce marijuana use, and taught us not to group together high risk youth for prevention interventions. Despite our progress, research gaps remain. For example, researchers are trying to determine what influences adolescent decision-making, especially decisions about drugs. What thoughts and emotions are going on at the precise moment an adolescent makes the initial and subsequent decisions to try or not to try drugs? These are questions that can not be answered by prevention researchers alone. A transdisciplinary and multi-pronged research approach that integrates all areas of science – basic behavioral, cognitive, developmental, social, neurobiological, and clinical – to develop innovative directions in drug abuse prevention research, is the underlying premise for NIDA's new National Drug Abuse Prevention Research Initiative. Testing the effectiveness of new and existing science based prevention approaches through multi-site trials conducted at the local community level will also be important in this endeavor.

TREATING ADDICTION TO NICOTINE AND OTHER DRUGS OF ABUSE

Tobacco use remains one of the greatest risk factors for cancer. It is addiction to the drug, nicotine, that drives the continued use of tobacco in this country and abroad, despite the known negative consequences. Smoking cessation remains among the most

successful and cost-effective approaches to reversing the tide of tobacco-related diseases, including cancer. New technologies and breakthroughs in neurobiology, such as the recent identification of the critical role that the gene tryptophan hydroxylase – an enzyme that produces the brain chemical messenger serotonin – plays in the initiation of smoking are providing new opportunities for NIDA and other NIH Institutes such as the National Cancer Institute to collaborate at the scientific and clinical levels. Developing novel and selective medications to better treat addiction to tobacco and other substances of abuse is of mutual interest to many in the private and public sectors. NIDA will continue to develop addiction treatments, especially treatments that are specifically tailored to adolescent populations, such as those being tested at our Teen Tobacco Treatment Research Center in NIDA's Intramural Research Program in Baltimore, MD.

Developing new and effective ways to treat all addictions continues to be a high NIDA priority. Both behavioral therapies, such as cognitive behavioral therapies that have been shown successful in reducing cocaine use, and pharmacological approaches, will continue to be supported by NIDA. NIDA's Medications Development Program is about to bring two anti-cocaine medications to Phase III Clinical Trials this year. Not only are the medications Selegeline and Disulfiram showing success in cocaine-addicted populations, but they show promise as potential treatments for methamphetamine addiction as well.

EXPANDING NIDA'S CLINICAL TRIALS NETWORK

Recognizing that the path leading from new findings to changes in clinical practice can be lengthy, and that millions of people across the country are in need of quality drug abuse treatment, NIDA has established an infrastructure to more rapidly and systematically bring new treatments to those in need. When research-based treatments such as the behavioral therapy, motivation enhancement, and the pharmacological therapy, buprenorphine-assisted detoxification, are proven to work repeatedly in small controlled settings, they are developed into treatment protocols by researchers and practitioners and undergo rigorous multi-site trials to determine their effectiveness in community-based treatment settings. Currently, more than 15 treatment protocols are being tested or about to be tested in the established multi-site trials across the country. In FY 2003 NIDA plans to expand this infrastructure to ensure greater geographic distribution, and to reach underserved populations and regions underrepresented in the health care system, including individuals who have mental illnesses, those suffering from HIV/AIDS or other infectious diseases, adolescents who may be in need of drug treatment, and Hispanic and other minority populations.

AIDS AND OTHER MEDICAL CONSEQUENCES

Considerable scientific progress has been made in understanding, preventing, and treating HIV/AIDS and other infections among drug users. For example, NIDA-supported researchers have made tremendous progress in our battle against the Hepatitis C Virus (HCV). HCV infection is a major public health problem with 60 percent of all

new cases of acute HCV infection attributed to syringe and needle sharing. One of the most critical problems in controlling HCV is the variability of the virus with more than 9 distinct types of virus known. NIDA researchers identified an antibody that can block HCV from binding to the CD81 receptor that is found in both liver and B cells. This may prove to be a useful therapeutic target. An antibody proven to block this receptor would have the potential of blocking HCV infection or modulating early infections in exposed persons by interfering with the Hep C viral life.

Given that the epidemiological patterns of drug abuse and risk behaviors are constantly changing and new infections of HIV and other blood-borne and sexually transmitted infections continue to emerge and spread, NIDA is encouraging researchers to apply new findings to develop new and improved approaches to prevent the acquisition and ongoing transmission of these infections, as well as strategies to improve access to diagnostic screening and care.

INTEGRATING TREATMENT INTO THE CRIMINAL JUSTICE SYSTEM

Drug abuse treatment has been shown to reduce drug use and its related criminal behavior. The majority of individuals in prisons have a drug problem that requires treatment. For these reasons many different approaches for bringing treatments into the criminal justice system have been tried, including treatment as an alternative to prison, drug courts, drug abuse treatment in prison settings and treatment in community settings after release. Outcomes for each approach vary. NIDA is establishing a research infrastructure to test models at multi-sites to establish a more integrated approach to the treatment of incarcerated individuals with drug abuse or addictive disorders. The National Criminal Justice Drug Abuse Treatment Research System will serve as the vehicle for blending public health and public safety approaches.

STRESS AND HOW IT INFLUENCES DRUG USE

Particularly relevant in light of the events of September 11 is the role stress plays in drug use and addiction. We are expanding our research to better understand the role that stress plays in initiation, escalation and relapse to drug use so we can develop more effective ways to manage and treat stress. While we know that people take drugs initially to experience their rewarding and pleasurable effects, we also know that they relapse to taking drugs even after long periods of abstinence, for entirely different reasons. Stress is identified by most patients as the predominant factor to relapse. People prone to relapse also identify the triggers of environmental cues associated with previous drug use, and the drugs themselves. We are just beginning to appreciate that each of these triggers may involve brain circuitry different from that involved in the initiation of use and each operates on its own pathway. For example, (**as seen in figure 1**) stress-induced relapse appears to involve the hypothalamo-pituitary-adrenal axis to release stress hormones such as CRF from the brain and cortisol (steroid) from the adrenal glands. In contrast, cue-induced relapse appears to involve portions of the amygdala; and drug-induced relapses involves the mesolimbic circuitry. By more clearly

defining the neural pathways that subserve each trigger for relapse, such as the activation of CRF in the brain, NIDA will be able to more strategically identify and develop prevention strategies, as well as new targets for addiction medications.

GOVERNMENT PERFORMANCE AND RESULTS ACT (GPRA)

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compared our FY 2001 results to the goals in our FY 2001 performance plan.

THE FORMIDABLE FORCE OF SCIENCE

Continued progress can be expected in curtailing drug abuse and addiction if we continue to capitalize on the strong research foundation that NIDA has established. Research is critical to all of our Nation's endeavors and there is hope in knowing that new and growing public health needs such as Addiction, AIDS, Bioterrorism, and Cancer, and Diabetes, and others, are being tackled head on with the formidable force of science.

I would be pleased to respond to any questions. Thank you.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Raynard S. Kington, M.D., Ph.D.
Acting Director, National Institute on Alcohol Abuse and Alcoholism

on

Fiscal Year 2003 President's Budget Request
for the National Institute on Alcohol Abuse and Alcoholism

I am pleased to present the President's budget request for the National Institute on Alcohol Abuse and Alcoholism (NIAAA) for Fiscal Year 2003, a sum of $418,487,000, which reflects an increase of $32,541,000 over the comparable Fiscal Year 2002 appropriation.

Alcohol-use disorders are among the most pervasive of the behaviorally manifested diseases. One-quarter of our Nation's urban hospital beds are occupied by patients with behavioral or physical problems stemming from alcohol use.[1] Nearly 14 million adults meet diagnostic criteria for alcohol abuse or dependence.[2] More than 18% of Americans experience alcohol abuse or dependence at some time during their lives.[3]

The consequences of alcohol misuse cost society $185 billion every year, $47 billion more than the annual cost of smoking.[3] Alcohol misuse affects every age group, from fetuses exposed to alcohol in the womb to the elderly, and it affects these age groups differently. It cuts across genders and minority groups, which also respond to alcohol's toxic effects differentially. All of these consequences are preventable.

ADVANCES IN PREVENTION RESEARCH

About half of the risk of alcoholism is genetic, but environmental factors -- peer pressure, culture, and community attitudes toward alcohol use, for example -- can attenuate that risk. NIAAA conducts research on neuroscience and on environmental and behavioral strategies designed to prevent abusive drinking and its consequences. Investigators develop and test interventions at the individual, community, and policy levels, in specific populations, age groups, and settings.

In the past year alone, we have made significant advances in these areas. For example, a community-wide approach that focused on reducing the supply of alcohol

available to youths achieved significant reductions in drinking by children and adolescents. Another program that took a comprehensive, community-wide approach to reducing drinking resulted in significantly fewer violent assaults and car crashes.

Preventing children and adolescents from drinking is a major focus of NIAAA's research, which reveals that people who start drinking early in life are more likely than others to become alcoholic. Behavioral scientists found that this increase in risk may be the result of a common pathology that underlies a number of behavioral disorders.

Epidemiologic data identify disease trends that require preventive interventions. NIAAA epidemiologists discovered a change in racial and ethnic trends in mortality rates of cirrhosis, the primary cause of which is alcohol misuse, by examining improved methods of reporting on death certificates. White Hispanic males now show a higher rate of deaths from cirrhosis than do Black non-Hispanic males, who were thought to have higher rates.

A collaborative epidemiology project by the NIAAA, the National Institute on Drug Abuse, and the National Institute of Mental Health is examining the burden of co-occurring alcohol, drug, and mental disorders and associated disabilities, world-wide. This NIH-funded World Health Organization project also is developing standardized methods of collecting, analyzing, and reporting resource utilization and costs of these diseases and disabilities in diverse cultural settings.

ADVANCES IN NEUROSCIENCE AND GENETICS RESEARCH

Intricate biological mechanisms are the intermediaries of alcohol's physical actions in the nervous system, which manifest themselves as behaviors toward alcohol. NIAAA's neuroscience and genetics research have generated significant findings in this area during the past year.

For example, NIAAA-supported researchers established preliminary evidence that increasing production of specific proteins in the brain through genetics techniques may some day have utility in reducing drinking. Investigators also strengthened the evidence that specific genes, on chromosomes 1 and 7, are involved in alcoholism.

Through a collaboration with the National Institute of Mental Health, our intramural researchers found that a genetic variation in the serotonin neurotransmitter system plays a role in the sensitivity of nerve cells to the toxic effects of alcohol. NIAAA's intramural researchers also found further evidence that some of the same mechanisms in the nervous system that regulate appetite for food may play a role in risk of alcoholism.

By understanding the interplay of biological and environmental factors that contribute to alcohol-use disorders, we are better positioned to identify markers for people and populations at risk, and points for pharmaceutical and behavioral interventions.

ADVANCES IN RESEARCH RELATED TO THE TOXICITY OF ALCOHOL

The tissue-damaging effects of alcohol are not limited to the nervous system. Alcohol is a toxin, and it can injure any tissue in the body, with significant medical sequelae; for example, liver disease, some kinds of cancer, and brain damage.

Among the tissues most vulnerable to alcohol's toxicity are those of unborn fetuses, whose nervous systems are particularly susceptible to alcohol's effects. The most severe outcome is fetal alcohol syndrome (FAS), which results in a lifetime of neurobehavioral deficits and disabilities. For the first time, using living mammalian models, investigators have found that administering two different, naturally-occurring substances, choline and nerve-growth factors, can prevent alcohol-induced brain damage to the developing fetus. This is a significant finding, since no treatment for FAS exists, currently.

Intramural investigators discovered a potential explanation as to why chronic, heavy drinkers are completely unresponsive to treatment for hepatitis C virus infection. Hepatitis C infection is a prevalent disease, particularly among alcoholics, and the current treatment of choice is expensive. Investigators found that a protein produced in response to inflammation suppresses the biochemical pathway of the drug used for treatment and boosts activity of the genes whose protein products block the effects of the treatment drug.

RECENT INITIATIVES

During the five-year doubling of the NIH budget, NIAAA has established major new initiatives designed to advance research in each of the areas essential to its mission.

The Integrative Neuroscience Initiative on Alcoholism (INIA) is advancing our understanding of alcohol's actions in the nervous system. INIA integrates findings from multiple disciplines, from the genetic to the molecular and behavioral levels. Our intramural program also established an integrative neuroscience research program that combines cellular and molecular biology studies, considered the most powerful approach to the neural basis of alcohol abuse and alcoholism.

We have established several initiatives that are enabling us to capture the potential of new genetics technologies. On the molecular level, an initiative that focuses on the use

of advanced instrumentation soon will enable our scientists to examine directly alcohol's interactions with the brain's neurotransmitter systems. In doing so, scientists can couple molecular events with behavioral events, in real time. This technology will provide essential information for our neuroscience research.

The initiatives described above are moving us closer to identifying optimal targets for therapeutic interventions. We have launched a major effort to develop medications that are more widely effective in treating alcohol abuse and alcoholism. Studies include tests designed to determine what types of patients respond favorably to currently available medications, and whether combining medications with specific behavioral therapies improves success rates.

The increases in the NIAAA budget also have enabled our intramural researchers to establish a liver biology program. Investigators in this program already have produced an important breakthrough; they have found that a specific protein of the immune system protects liver cells from the toxic effects of alcohol. NIAAA recently established two new initiatives on alcohol-related liver disease.

Because some minority groups and women appear to suffer disproportionately from alcohol-induced organ damage, such as liver disease, we have established an initiative to study disparities in alcohol toxicity. A recently established collaborative initiative focuses on FAS prevention. Prominent in these investigations are studies of specific minority groups, such as Native Americans and African Americans, who are disproportionately affected by FAS.

We also are stimulating research to develop biomarkers that detect early, alcohol-induced toxic changes in cells. Another initiative is to develop a biosensor that monitors alcohol levels continuously, to elucidate how drinking behaviors lead to organ damage.

Our prevention program is conducting studies to assess whether interventions that have proven to be successful in majority populations also are effective for specific minority groups. The program also encourages research that examines whether high-alcohol-content, low-cost beverages, such as malt liquor, disproportionately affect minorities.

Youth is a special focus of our prevention research, and the initiatives we have established over the past five years include a major effort to prevent alcohol problems among college students and another to prevent alcohol use among young adolescents. College drinking is more destructive than previously recognized, and the NIAAA

Council's Task Force on College Drinking has brought together the college and research communities in an unprecedented national dialogue.

OUTREACH

Ultimately, NIAAA's research is intended to benefit the public's health. We attempt to achieve that goal in a number of ways. For example, our Research to Practice Initiative is a collaboration between NIAAA and the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment. Representatives from these two agencies meet with treatment providers and administrators to exchange information about current research findings and obstacles to providing treatment that practitioners encounter. The agencies then arrange for experts to serve temporary residencies in treatment programs, to ensure success.

Women of child-bearing age are the focus of the D.C. Initiative, a major effort to prevent FAS in the District of Columbia, which has one of the Nation's highest FAS rates. The project is designed to prevent drinking among African-American women who are pregnant or can become pregnant.

On April 9, after three years of investigations, the NIAAA Council's Task Force on College Drinking will release a report that includes recommendations for colleges, researchers, and communities. NIAAA will hold regional workshops that will involve 3,200 colleges, and will provide brochures for parents, college administrators, high-school guidance counselors, and community leaders. Papers and panel reports that served as the basis for the Task Force's report will be published in scientific journals; for example, a supplement to the April 2002 issue of the *Journal of Studies on Alcohol*, on college drinking, will include 18 review articles adapted from papers commissioned by the Task Force. An interactive NIAAA website serves as a resource for college personnel, researchers, and the public.

Alcohol Screening Day, a nationwide event sponsored by the NIAAA, enables people to receive free screening for alcohol problems and, if needed, referrals. This year's Screening Day will take place on April 11. We anticipate more than 2,000 participating sites, more than half of which will be college campuses.

We are reaching children and adolescents through our *Leadership to Keep Children Alcohol-Free*. Thirty-three State governors' spouses have joined this project to reduce drinking by young people; a crucial effort, given our research findings that early initiation of drinking portends higher risk of alcoholism later in life. We also are preparing public service announcements on underage drinking.

GOVERNMENT PERFORMANCE AND RESULTS ACT

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) Of 1993. Prominent in the performance data is NIH's third annual performance report, which compares our FY 2001 results to the goals in our FY 2001 performance plan. As performance trends on research outcomes emerge, the GPRA data will help NIH to identify strategies and objectives to continuously improve its programs.

[1] Moore, RD; Bone, LR; Geller, G; Mamon, JA; Stokes, EJ; Levine, DM Prevalence, detection, and treatment of alcoholism in hospitalized patients. *Journal of the American Medical Association* 261(3):403-407, 1989.

[2] Grant, BF et al. Prevalence of DSM-IV alcohol abuse and dependence: US, 1992. *Alcohol Health and Research World* 18(3):243-248,1994.

[3] Updated estimate by the Lewin Group, October 1999, of Harwood, H., et al. *The Economic Costs of Alcohol and Drug Abuse in the US*, 1992. National Institute on Drug Abuse, 1998. US Dept. of the Treasury. *The Economic Costs of Smoking in the US and the Benefits of Comprehensive Tobacco Legislation*, Washington, DC, 1998.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Patricia A. Grady
Director, National Institute of Nursing Research

on

Fiscal Year 2003 President's Budget Request
for the National Institute of Nursing Research

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Institute of Nursing Research for FY 2003, a sum of $130,809,000, which reflects an increase of $10,058,000 over the comparable Fiscal Year 2002 appropriation.

For over a century, the nurse's role in care of the sick has been well known, especially in times of war or disasters. What is also important in this new century is the role of nurse as scientist – bringing to the scientific process an additional perspective critical to health, examples of which will be highlighted today. Our science is young, yet it is already making innovative changes to practice. These contributions were evident as NINR celebrated its 15th anniversary at the National Institutes of Health with a scientific symposium that featured nursing research programs of excellence.

The nursing shortage, however, which is capturing national attention, is emerging just when challenges to the healthcare system are increasing. Therefore, it is critical that nursing research produce results that improve health and quality of life for the American people. Innovative strategies to address these challenges must be identified, and they must be scientifically tested.

RESEARCH TO HELP CAREGIVERS

Major challenges for healthcare are the increase in age of our population, the increase in chronic illness, and the earlier discharge of patients from hospitals, which, taken together, have created a greater need for informal caregivers. These caregivers are generally family members, friends, or neighbors. According to the 1997 National Caregiver Survey by the AARP, more than 22 million adults are informal caregivers to ill or fragile Americans over 50 years of age. A study of informal caregivers, published in 1999 in *Health Affairs*, indicates that most caregivers are middle-aged, married women, almost half of whom have young children. They provide most of the long-term care in our country, yet the economic value of their services, estimated at $196 billion in 1997, is not included in cost of illness figures. The healthcare system, in effect,

depends on their collective assistance. Research to address caregiver issues is critical at this important juncture.

In addressing these issues, nursing research has focused on helping caregivers avoid or reduce their burdens, including stress, especially related to chronic illnesses, such as dementia, emphysema, and congestive heart failure. Caregivers must manage disruptive behaviors, including wandering, aggression, and sleep-wake disturbances, and they may be required to administer medication and use unfamiliar equipment, such as suctioning devices and ventilators. NINR-supported research also identifies caregiver techniques to improve their own health and quality of life.

Although subgroups of caregivers characterize their situation as a positive experience, there is also a high incidence of stress among caregivers that can lead to depression, physical illness, and increased mortality. A recently published study of a community-based 14-hour training program for caregivers, held during a two-week period, found that three months after the training, 25 percent of participants reported lower levels of depression, 28 percent reported improvement in behavioral problems of their care recipients, and 9 percent indicated that they felt less burdened. This brief intervention provided caregivers with information and practical skills for dealing with dementia, and ways to improve confidence, coping skills, and communication. The results are illustrative of the possibilities of using coaching and teaching to reduce the negative effects of caregiving. Further research is needed to identify techniques that work best – for example, those that can be generalized and those that may only apply to specific situations.

RISKS OF UTERINE RUPTURE IN FUTURE PREGNANCIES FOLLOWING INITIAL CESAREAN BIRTH

A recent study published in *The New England Journal of Medicine* has captured the public's attention. This study demonstrated that cesarean delivery can increase the risk of uterine rupture during labor in a subsequent pregnancy. Researchers analyzed records of over 20,000 women who gave birth to a second child after an earlier cesarean delivery. The risk of uterine rupture when having a second cesarean delivery with no labor is 1.6 per 1,000 births. The risk of rupture during spontaneous labor for this population is over three times as great, and if prostaglandins are used to induce labor, the risk increases 15 fold. Since 60 percent of women with prior cesarean deliveries attempt labor with the next pregnancy, this is important information for use in patient education. Mothers-to-be also need to know that initial cesarean delivery will affect future births.

LEARNING DEFICITS IN CHILDREN TREATED FOR ACUTE LYMPHOBLASTIC LEUKEMIA

For children with Acute Lymphoblastic Leukemia, who now have considerably improved long-term, disease-free survival rates, there are also long-term consequences,

including academic difficulties caused by aggressive, life-saving treatments. These treatments involve the central nervous system and include whole brain radiation and high dose chemotherapy. Nursing research has shown that these children have declines in arithmetic, verbal fluency and visual and motor-related skills, which affect their success in school. Young survivors showed these deficits for up to four years after their treatment regimens ended. A pilot study testing a remedial math intervention to minimize this type of deficit has shown early positive results. A larger study to test this intervention is now in progress.

REDUCING RISKS OF A SECOND CARDIAC ARREST

In addition to finding ways to reduce or eliminate treatment side effects, nursing research also examines how to lower risks accompanying disease. Preliminary results of a biobehavioral intervention on patients who had cardiac arrest showed that there was an 86 percent reduction of mortality from cardiovascular disease in these patients for up to two years. The intervention consisted of training in physiological relaxation using biofeedback; coping skills for depression, anxiety, and anger; and health education about cardiovascular risks. Although the underlying reasons for these positive results are not fully understood, it is hypothesized that decreases in psychological distress improve cardiovascular prognosis. This study underscores the importance of biobehavioral approaches for survivors of cardiac arrest.

NEW AND EXPANDED INITIATIVES

In FY 2003, NINR plans to expand activities that address the health disparities prevalent in our society by incorporating such factors as ethnicity, culture, gender, socioeconomic status, and geography. This area has always been an important tenet of nursing science and is one of its special strengths. Since ethnic minority groups have a number of health problems associated with higher morbidity and mortality rates than do majority groups, NINR will continue to focus on these issues. A major new emphasis will be on community research partnerships in which community members help to identify and address key health concerns. A workshop to delineate possible research areas and strategies was held earlier this year to begin this activity.

As the Committee is aware, NINR is advancing research on end-of-life and palliative care, and is the lead coordinator of NIH research in this area. In addition to investigating new models for palliative care, next year we plan to focus on pediatric and genetic end-of-life issues, with continued efforts to include minorities in our research programs.

Next year NINR will expand the research agenda to address care issues for residents in long-term facilities, such as nursing homes and assisted living. The number of assisted living residents is projected to increase from approximately 1 million in 1998 to more than 1.7 million in 2025, according to the National Center for Assisted

Living. NINR plans to solicit studies that deal with issues such as residents' functional mobility, transitional problems in adjusting to their loss of independent living, and prevention of falls and depression,

Another emphasis is health promotion for adolescents to reduce their high-risk behaviors that will affect their health later in life. We will encourage studies that test health promotion interventions to decrease smoking, substance abuse, and risky sexual behavior, and improve nutritional status in school, at work, and in community-based settings. Research to test culturally and linguistically appropriate interventions involving ethnic minorities will provide valuable answers to address these problems.

Since nursing research is important to improve better health, it is imperative that NINR work at building future capacity. The nursing shortage will impact nursing research by reducing the number of investigators available to conduct studies that add to the scientific base for practice. To ensure a stable research workforce for the future, NINR plans to use several new approaches, including earlier entry to research careers. Research career development of minority nurses will be emphasized to enhance research on health disparities. One innovative strategy is being carried out in collaboration with the new National Center on Minority Health and Health Disparities. Together we developed pilot research partnerships between established research intensive institutions and minority-serving institutions. The goal was to increase diversity in the nurse researcher pool and to increase research to reduce health disparities. The second phase of this activity is currently under way and shows much promise.

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compared our FY 2001 results to the goals in our FY 2001 performance plan.

In closing, we are in a high pressure period of increasing demands for empirically based nursing care, while facing a possible diminution of both nurses and nurse researchers. Research provides career challenges for nurses that will stimulate their intelligence, their empathy, and their energy. Nursing research offers the opportunity to enhance the health for all of our Nation's people.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Francis S. Collins
Director, National Human Genome Research Institute

on

Fiscal Year 2003 President's Budget Request
for the National Human Genome Research Institute

Mr. Chairman and Members of the Committee:

During Fiscal Year 2003, the field of genetics will observe a major anniversary, and the National Human Genome Research Institute will reach an unprecedented accomplishment. Fifty years ago, in the spring of 1953, Drs. James D. Watson and Francis Crick reported the discovery of the double helix structure of DNA, a landmark achievement in the annals of scientific research. In 2003 the Human Genome Project expects to complete the final DNA sequence of the human genome. NHGRI and their partners in the International Human Genome Sequencing Consortium announced the working draft of the human genome sequence in June 2000, published the initial analysis in February 2001, and since then have been working to correct all the remaining spelling errors and fill in all the gaps. The Human Genome Project is on target to meet that deadline and expects to finish the analysis in time for the 50th anniversary of the Watson-Crick paper.

The availability of the genome sequence of humankind could be said to mark the starting point of the genome era in biology and medicine. There is now much important work to do to deliver on the promise that these advances in genomics offer for human health. While sequencing the human genome has been NHGRI's most visible goal, the Institute has also been conducting important genetic and genomic research in a variety of areas, including working to understand the way individuals differ from each other at the genetic level and the impact these variations may have on health. In addition, the Institute leads in the development of new technologies, such as DNA chips and tools for proteomics, and has been creating novel research strategies to study the function of genes and genomes.

A NEW RESEARCH PLAN FOR NHGRI

The Human Genome Project has, since its inception, been guided by a series of overlapping 5-year plans. These plans have laid out ambitious goals to advance our understanding of the human genome and the associated ethical, legal and social implications. The plans have been instrumental to the success of the Project by clearly enumerating our program objectives to the scientific community and the public, and by providing measurable objectives to guide our work and gauge our progress and success.

In December 2001, the NHGRI convened about 200 experts, including scientists, researchers in the ethical, legal, and social implications (ELSI) of the Human Genome Project, consumers, and policy experts to think very broadly and creatively about the future of genomics. Over the course of the following months, we will host several workshops to explore specific topics in detail and enumerate specific goals appropriate for NHGRI. We will take stock of where we are and where we have come from, critically evaluating the challenges and opportunities that lie before us and creating a bold new vision for the future of genomics.

EARLY AND STUNNING RESULTS FROM THE HUMAN GENOME SEQUENCE

Obtaining an accurate reference version of the human sequence has always been the most compelling goal of the Human Genome Project. Between March 1999 and June 2000, the production of human genome sequence data in Institute-supported laboratories skyrocketed. During this time, scientists sequenced 1,000 DNA letters a second--24 hours a day, 7 days a week. The resulting working draft sequence covered over 94 percent of the human genome, with 33 percent in highly accurate finished form by February 2001. By January 2002 the amount in highly accurate finished sequence had risen to 65 percent. The final sequence will be completed in 2003, two years ahead of the original ambitious schedule.

The draft sequence of the human genome is already having a major impact on biomedical research. In the 12 months following the February 2001 publication in *Nature* of the publicly funded draft sequence, the paper has been cited in over 700 scientific reports, making it one of the most cited papers in all of science for the past year. These citations clearly demonstrate the widespread utility of the publicly available genome sequence and its enormous early impact to advance biomedical research in a wide array of areas.

The rationale for the Human Genome Project, and the strong and sustained Congressional support for it, has been the promise of improving human health. We are already beginning to see the fruits of that investment. Some of the citations of the *Nature* publication represent research that could not have been accomplished in nearly the same way or would not have been as profound were it not for the draft sequence of the human genome. More than 50 genes involved in human disease have been discovered, based on access to the public human genome sequence data. The examples cited below show the direct connection the genome sequence is having on improving human health.

Prostate Cancer

Using the draft sequence of the human genome, scientists at Johns Hopkins University and the NHGRI have found the first gene associated with an inherited form of prostate cancer. In a study of 91 high-risk prostate cancer families the researchers mapped the first hereditary susceptibility to prostate cancer to a region of chromosome 1 that they called the Hereditary Prostate Cancer 1 Region, or HPC1. They have now identified a specific gene – called RNASEL – in the HPC1 region that contains DNA misspellings associated with prostate cancer. Misspellings in this one gene do not explain all forms of inherited prostate cancer, but the discovery of this gene is an exciting step towards understanding the causes of this common and devastating form of cancer. Ultimately, this discovery should bring us closer to being able to prevent the disease as well as better diagnostics and treatments.

Kidney Disease Gene
The recent identification of the gene for autosomal recessive polycystic kidney disease (ARPKD) by a team at the Mayo Clinic again shows the great power of the draft human sequence. The publicly available sequence of the human genome played an important role in the discovery of this disease-causing gene. With the identification of the responsible gene and the characterization of a rat model of the disease, rapid progress in understanding ARPKD can now be anticipated.

THE FUTURE OF GENOMICS

The Human Genome Project and the NHGRI have always aimed to develop new information, tools and technologies that would enable scientists to gain a deeper understanding of the genetic contributions to disease, and to use this knowledge to improve human health. The imminent completion of the project's initial goals presents a compelling opportunity to focus aggressively on translating the spectacular research advances into medical advances. With the completion of the Human Genome Project soon at hand, much additional basic research, guided by a genomic approach, remains to be done to shed light on the many mysteries of life. At the same time, genome research offers a myriad of other opportunities for connecting detailed knowledge of the human genetic instruction book with important problems in clinical research. These basic and applied paths are not mutually exclusive, and finding the right balance between them, although challenging, will be the most effective approach in the end.

Comparative Genomics
To understand the function of the human genome sequence, scientists would like to compare it to the genome sequences of many other organisms. This approach relies on the fact that functionally important regions of DNA are conserved over long periods of evolutionary time. By comparing the human genome sequence with those of the rat, mouse, and other organisms, similar regions are readily apparent, indicating that something biologically interesting – such as the existence of a gene or important regulatory element – must be present at that location of the genome.

Simplifying the Study of Complex Genetic Diseases: The Haplotype Map of the Human Genome
Prior to the completion of the draft sequence of the human genome, most studies of diseases using genetics focused on single gene disorders such as cystic fibrosis and Huntington's disease. With the tools of the Human Genome Project, finding the genes for diseases caused by alterations in single genes has become relatively straightforward. Many common diseases, however, such as diabetes, cancer, heart disease, psychiatric disorders, and asthma are influenced by complex interactions between multiple genes as well as by non-genetic factors such as diet, exercise, smoking, and exposure to toxins.

A key next step of the Human Genome Project will be the generation of a "haplotype map" of the human genome. This comprehensive resource for human biomedical research will capture the complete catalogue of the common genome ancestral segments--"haplotype blocks"--observed in the major human populations. This map will provide a new tool for scientists to scan the entire genome and identify more rapidly and effectively those genetic variations associated with disease risk and drug response in the human population. That, in turn, will help researchers develop an understanding of the complex biological processes that give rise to the

disease and assist scientists in discovering treatments or cures for these illnesses. This new and exciting project is expected to be a public-private partnership and the data will be immediately and freely accessible.

Health Disparities Strategic Plan
From its inception NHGRI has been concerned about including individuals from various groups in its activities. As the Institute has grown in size and complexity the need for this has become even more imperative and a variety of initiatives have been started and continue to evolve to address this need. The NHGRI staff recognizes the inherent value of increasing diversity among the research workforce as well as engaging and empowering people from minority communities through joint research projects, information sharing, dialogue and the development of partnerships. In order to achieve these goals, NHGRI has developed a plan that lays out a multifaceted approach to address issues of health disparities. The plan encompasses research, training, and education/outreach activities.

ETHICAL, LEGAL AND SOCIAL IMPLICATIONS

From its inception, NHGRI has taken on the responsibility to address the broader ethical implications of rapid advances in genetic information and technology. Since 1991, it has committed 5 percent of its budget to studying the ethical, legal, and social implications (ELSI) of genome research.

The ELSI Research Program has continued to support significant and innovative research on the ethical, legal, and social implications of human genome research. Research projects supported in FY 2001 included projects in the areas of the privacy and fairness in the use and interpretation of genetic information; clinical integration of new genetic technologies; issues surrounding genetics research; and public and professional education.

As the Institute develops its new research plan, the ELSI issues will be carefully integrated. It will be extremely important to consider these issues as new fields of genomic discovery appear. It will also be essential for ELSI funded research to inform policy development in the area of genetics.

EDUCATION AND OUTREACH

National Coalition for Health Professional Education in Genetics
In 1996, along with the American Medical Association and the American Nurses Association, the NHGRI founded the National Coalition for Health Professional Education in Genetics as a national effort to promote health professional education and access to information about advances in human genetics.

NHGRI/ORD Genetic and Rare Diseases Information Center
There are more than 6,000 genetic and rare diseases afflicting more than 25 million Americans, but many of these illnesses affect relatively few individuals. As a result, information about these rare disorders may be limited or difficult to find. In order to respond to this need, the NHGRI and the Office of Rare Diseases (ORD) have established

the NHGRI/ORD Genetic and Rare Diseases Information Center to provide information on genetic and rare disorders to the public. The Information Center will meet the ever-increasing information needs of the general public, including patients and their families, health care professionals, and biomedical researchers by: 1) serving as a central, national repository of information materials and resources on genetic and rare diseases, 2) collecting and disseminating information on the diagnosis, treatment, and prevention of genetic and rare disorders, and 3) coordinating with organizations and associations interested in genetic and rare disorders.

CONCLUSION

The investment in the Human Genome Project is already paying off in terms of advances in biomedical science that promise unprecedented advances in human health. We are moving into a new phase of genomics which will give us a deeper understanding of the genetic contributions to disease. Our vision is that by focusing on the applications of genetics to human health we will make great strides towards treating and curing many complex diseases.

The NIH budget request includes the performance information required by the Government Performance and Results Act of 1993. Prominent in the performance data is NIH's second annual performance report which compares our FY 2001 results to the goals in our FY 2001 performance plan.

Mr. Chairman, I am pleased to present the President's budget request for the National Human Genome Research Institute for Fiscal Year 2003, a sum of $466,695,000, which reflects an increase of $35,977,000 over the comparable Fiscal Year 2002 appropriation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Donna J. Dean, Acting Director
National institute of Biomedical Imaging and Bioengineering

on

Fiscal Year 2003 President's Budget Request
for the National institute of Biomedical Imaging and Bioengineering

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) for FY 2003, a sum of $121,378,000, which reflects an increase of $9,356,000 over the comparable Fiscal Year 2002 appropriation.

Over the past year, it has been my privilege to preside over the formation and early development of the NIBIB, striving to provide a new and enriched focus at the National Institutes of Health (NIH) for bioengineering and imaging sciences. I can report to you today that, with help and support from the trans-NIH community, the NIBIB has taken significant steps in creating a research program in biomedical imaging and bioengineering that Congress envisioned when passing the NIBIB Establishment Act in December 2000.

MILESTONES TO SUCCESS

Guided by legislative language, and with input from the biomedical imaging and bioengineering communities, a mission statement was developed in March 2001, to articulate the NIBIB overall vision, goals and objectives. Upon my appointment as Acting Director in April, I was able to focus immediately on NIBIB's future as defined by the mission - "to improve health by promoting fundamental discoveries, design and development, and translation and assessment of technological capabilities in biomedical imaging and bioengineering, enabled by relevant areas of physics, chemistry, mathematics, materials science, information science, and computer sciences". Our Institute will foster and support an integrated and coordinated program of research and research training that can be applied to a broad spectrum of biological processes, disorders and diseases and across organ systems.

The foundation upon which the NIBIB will build its success comes from the applications submitted by investigator-initiated research. NIBIB staff worked with the NIH Center for Scientific Review to implement referral guidelines and procedures so that applications relevant to the NIBIB mission would be appropriately directed to the Institute. In addition, Institute staff monitored the ongoing peer review process for grant applications already in the pipeline that would be eligible for NIBIB funding.

In accordance with the NIBIB mission to foster trans-NIH collaboration, the administration of the NIH Bioengineering Consortium (BECON) was transferred to the NIBIB. The BECON has been in existence since 1997 and has served as the focus of bioengineering extramural research at the NIH. The Consortium consists of senior-level representatives from most of the NIH Institutes and Centers (ICs) as well as representatives of other Federal agencies concerned with biomedical research and development. NIBIB joins the BECON as an additional institute representative and, in its administrative role, is committed to maintaining the successful coordination of trans-NIH bioengineering research, training, and communication programs.

The NIBIB is committed to supporting collaborations with other Federal agencies, and outside organizations, as indicated in our mission, to promote translation of cross-cutting technologies in bioengineering and imaging into biomedical applications. For example, the NIBIB and the Department of Energy (DOE) partnered to sponsor a workshop on "Applications of Thermography in Medical Diagnosis and Therapy", which served to identify clinical applications of the technology and to facilitate research partnerships between the DOE national laboratories and NIH investigators. In addition, with support from the NIBIB and the Institute of Electrical and Electronics Engineers (IEEE), the "International Symposium on Biomedical Imaging: Macro to Nano" will take place this July. These activities provide a forum to showcase current technology and applications, identify future biomedical needs and the emerging technologies, and assist in the process of planning the future research agenda.

On October 1, 2001, the NIBIB announced its establishment to the public through the launch of the official Institute website (http://www.nibib.nih.gov). The site serves as a conduit of information for those with an interest in the Institute and the fields of biomedical imaging and bioengineering. Comprehensive information about the history, mission, legislative activities, budget, staff, vacancy announcements, research and training opportunities and the administration of the Institute is available on the website. To date the website has received almost 700,000 hits from over 22,000 individuals and groups. Feedback indicates that the website is reaching a wide audience and providing useful information.

In addition, significant efforts are being made to communicate directly with the groups that look to the NIBIB for research support. We have targeted outreach activities specifically for engineering, physical and quantitative science communities,

many of whom may be new to NIH programs and procedures. As Acting Director, I have made presentations across the nation to organizations that represent biomedical imaging and bioengineering communities. In addition, our staff have attended numerous meetings to inform the scientific communities about the NIBIB mission and current and planned research opportunities. For example, in recent months, we have met with academic, industrial, and government representatives in the states of Connecticut, Hawaii, Kentucky, New York, Pennsylvania, North Carolina, Indiana, California, and Virginia to discuss the development of consortia that support regional economies and multi-disciplinary biomedical research programs.

BUILDING A RESEARCH PORTFOLIO

The overarching goals of the NIBIB research program are to develop fundamental new knowledge, foster potent new technologies, facilitate cross-cutting capabilities and nurture a new generation of researchers. To that end, several scientific areas have been identified for targeted research that is uniquely suited to the NIBIB mission. Among these are microtechnology and nanotechnology, diagnostic imaging, molecular- and cellular-level imaging, biosensors, biophotonics, materials, computational biology and computer technology. In addition, the training portion of the NIBIB mission will involve facilitating training programs for scientists with backgrounds that combine the biological and medical sciences with the allied engineering and physical science disciplines to develop the expertise they will need to carry out biomedical imaging and bioengineering research in the years to come. The next phase of building the NIBIB research and research training portfolio involves developing initiatives that will stimulate activities in these areas.

As one of the first steps in building the NIBIB research portfolio, scientific staff worked to identify ongoing research programs within the other NIH Institutes and Centers (ICs) involving areas of biomedical imaging and bioengineering that would be appropriate for NIBIB participation. For example, the "Bioengineering Research Partnerships" Program Announcement (PA) solicits applications from researchers seeking to establish multi-disciplinary research teams to address a significant area of bioengineering research within the mission of NIH. Another PA, "Technology Development for Biomedical Applications," invites applicants who are developing novel instruments, devices, methodologies and software for use in biomedical research. In order to form partnerships with other ICs as articulated in our mission, the NIBIB has joined a variety of other initiatives across NIH.

To further enhance our research portfolio, the NIBIB is proud to announce our first two scientific initiatives in the areas of biomedical sensors and molecular-level imaging. Biomedical sensors can be defined broadly as devices that detect specific molecules or biological processes and convert this information into a signal. Biology

and medicine have gained enormous insight into the life process by discovery, development and application of sensors. To advance this technology, the NIBIB recently issued a Request for Applications (RFA) entitled "Sensor Development and Validation." The purpose of the RFA is to support basic and applied research targeted at sensor development. In addition, the NIBIB will be the lead sponsor of an international assessment of the status of biosensor technology along with several other Federal agencies.

Discoveries in molecular and cellular biology present extraordinary opportunities for biomedical imaging to play an important role in the early detection, diagnosis and treatment of disease. The support of fundamental discovery and technical development of imaging technologies, before specific disease- or organ-oriented applications are determined, is critical, and is highlighted in the NIBIB mission. Another RFA recently issued by NIBIB, entitled "Research and Development of Systems and Methods for Molecular Imaging," addresses this important scientific need, and will support novel investigations for development of molecular imaging and spectroscopy that can be applied to multiple biological or disease processes.

The NIBIB's current portfolio supports a broad range of cross-cutting biomedical research and enabling technology development in areas such as biomaterials that encourage neural regeneration, microneedles for painless drug delivery, high-resolution imaging of soft tissue, and sensor microarrays for instantaneous chemical identification. (see Appendix)

FUTURE STRATEGIES

In the upcoming year, the NIBIB will begin to focus its research agenda and develop programs in such areas as nanotechnology and reparative medicine. Many scientists believe that nanotechnology is a new field of research that will enable the development of a new generation of scientific and technological approaches, as well as tools and devices used in research and clinical settings. One area where nanotechnology could be applied to medical therapy is the development of nanoparticle materials for drug discovery, production, and delivery. Nanoparticle materials offer significant improvements in bioavailability and efficiency through oral and injectable pathways. Since cellular- and molecular-level interactions occur on the nanometer scale, such technologies have the potential to offer significant improvements over current treatment options. The NIBIB plans to stimulate research in this area, based on recommendations from the 2000 BECON symposium entitled, "Nanoscience and Nanotechnology: Shaping Biomedical Research".

Reparative medicine represents a critical and highly visible frontier in biomedical and clinical research. A key component of the field is tissue engineering, the goal of which is to repair or replace tissues and organs by delivering DNA, proteins, protein

fragments, implanted cells or scaffolds to areas where they are needed. The NIBIB has a role in this endeavor to explore the following areas: self-monitoring materials for cell-, drug-, or gene-based therapies; predictive, low-cost *in vivo* and *in vitro* models; accelerated testing and failure analysis; and approaches to understanding the biology-biomaterial interface. In accord with recommendations from the 2001 BECON symposium entitled, " Reparative Medicine: Growing Tissues and Organs", we are developing initiatives to address these needs.

Other areas presenting rich opportunities for NIBIB research are included in our plans for future programs. In imaging device development, we plan to support research and development of generic biomedical imaging technologies before specific applications are demonstrated. In implant science, critical needs are development of tools for assessing loads and stresses in an operating environment, rapid simulation and prototyping methods and life-time predictive methods for design and analysis at the time of implant design, and during dysfunction and failure. Imaging processing and analysis offer challenges in the development, design, and implementation of image acquisition and information analysis algorithms, image-guided procedures and techniques for deriving physiology and function from multidimensional images.

Planning for a research training program is a high priority for the NIBIB, considering the recent Department of Labor report which indicated that biomedical engineering jobs would increase by more than 31 percent by the end of the decade. To determine needs in trans-disciplinary training, the NIBIB participated in a joint NIH-National Science Foundation (NSF) workshop on training and education in the fields of bioengineering and bioinformatics that brought together researchers and educators from across the nation. Preliminary plans include funding for multiple components at all career levels, including experiences at the pre-doctoral and post-doctoral levels, a summer training experience for quantitative science students, and institutional grants through the NIH National Research Service Awards (NRSA) program. Our goal is to facilitate the trans-disciplinary training and education necessary to assure the availability of future generations of highly-trained professionals to meet the anticipated national demands.

As a dynamic and synergistic Institute, the NIBIB is pleased to be a part of the Federal science and technology research enterprise in the 21st century high-tech information age. We look forward to establishing our role in this important endeavor.

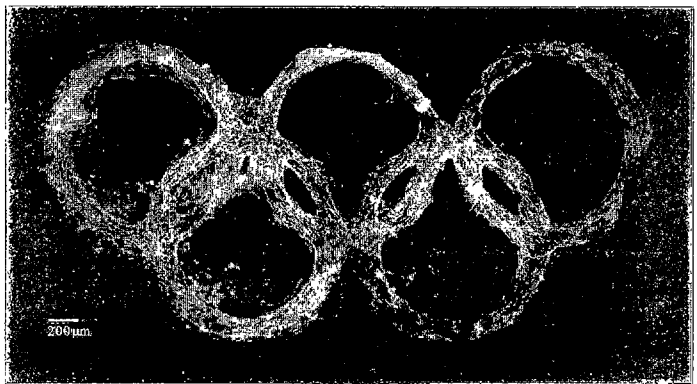
Mr. Chairman, I would be pleased to answer any questions you or the Committee may have.

Appendix

Examples of Research Supported by the National Institute of Biomedical Imaging and Bioengineering

Probing Single-Molecule Neuron-Ligand Pathfinding (8-R01-EB00463-02)

Principal Investigator: **Thomas Beebe,** University of Delaware



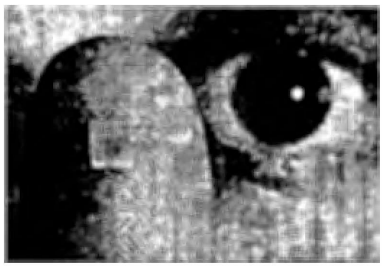
Nerve cells and fibers grow on a bioengineered scaffolding in the shape of the Olympic rings in a demonstration of technology that someday may help people with brain disorders and spinal cord injuries. The "living rings" measure about one-eighth-inch wide.

Source: Beebe, T. University of Delaware

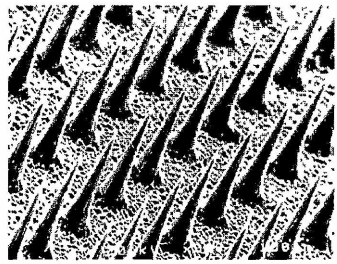
(pending approval of image usage from Principal Investigator)

Microfabricated Microneedles for Drug Delivery (8-R01-EB00260-03)

Principal Investigator: **Mark Prausnitz,** Georgia Institute of Technology



Size of experimental microneedle array is shown by its placement on the researcher's finger. There are 400 needles in the array.

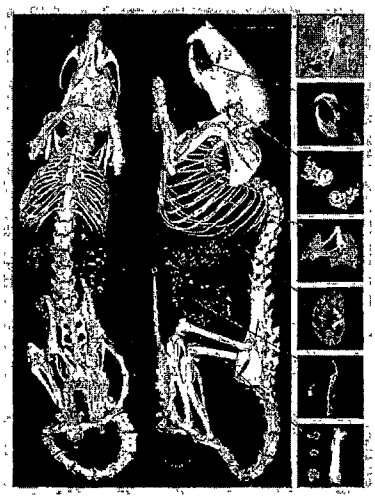


Electron micrograph close-up of the needles, with added color.

Source: Photographs are copyrighted by the Georgia Tech Research Corporation and may be freely used by the news media with credit to the Georgia Institute of Technology. The photographer is Stanley Leary, Georgia Tech Communications Division.

Multidisciplinary Micro CT-3D Imaging Facility (8-R01-EB00305-06)

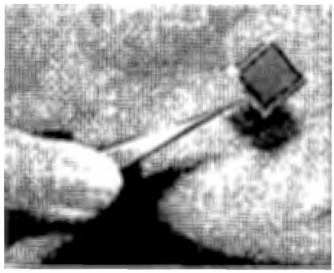
Principal Investigator: **Erik Ritman,** Mayo Clinic

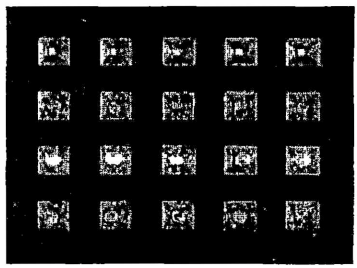


Source: Copyright © 1996-2002 Mayo Foundation for Medical Education and Research.

Development of an Electronic Tongue (2-R01-EB57306-04A1

Principal Investigator: **Eric Ansyln,** University of Texas





Source: University of Texas.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Judith L. Vaitukaitis
National Center for Research Resources

on

Fiscal Year 2003 President's Budget Request
for the National Center for Research Resources

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 2003, a sum of $1,091,374,000, which reflects an increase of $78,836,000 over the comparable Fiscal Year 2002 appropriation.

We cannot do today's science with yesterday's tools. As director of the National Center for Research Resources, I hear regularly from the scientific community that to do quality work, scientists must have access to state-of-the-art research tools and technologies. NCRR provides the biomedical research community with the research tools, specially designed research facilities, biologic models of human disease and other resources necessary for studies that define the causes of human disease. I am pleased to have this opportunity to share with you recent research contributions made possible by NCRR-funded programs, and to outline our future plans for facilitating biomedical discovery through development of novel technologies and strategic provision of research resources.

NCRR's crosscutting research resources transcend the entire spectrum of scientific inquiry funded by the institutes and centers within the National Institutes of Health (NIH). Each year more than 28,000 investigators, supported by more than $4 billion in competitive grants from other NIH components, as well as from other Federal agencies and the private sector, use NCRR-supported research resources to conduct their studies. To get the most out of dollars committed to research resources, NCRR encourages investigators and institutions to share scarce or expensive research resources. In addition, NCRR supports research resource facilities for both basic and clinical research that are shared institutionally, regionally or nationally. Those include networks for General Clinical Research Centers (GCRCs), Regional Primate Research Centers, Biomedical Technology Resource Centers, Research Centers in Minority Institutions, and many other resources, including bio-repositories---all essential to NIH-supported research. The clinical research settings of the GCRCs allow countless investigations of human diseases, both rare and common. The biologic models validated and supported by NCRR have exposed many of the basic mechanisms that underlie human disorders. NCRR-funded technology resources have broad-ranging applications, ranging from molecular structures to views of the brain affected by degenerative processes, including Alzheimer's and Parkinson's diseases. Other resources include those for generating vectors for human gene transfer, and centers for isolation

of human pancreatic islet cells for transplantation into patients with Type 1 diabetes mellitus. Resource sharing is a cost effective approach to funding biomedical research.

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 and biomaterials with greater sensitivities and much higher throughputs. 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. Today MRI is an essential clinical tool, saving countless invasive surgical procedures each year. NCRR supported the development of MRI from its earliest iterations---as an obscure technology used only in chemistry labs---to the clinical tool that physicians have come to depend on. NCRR continues to support the evolution of MRI and other technologies, including mass spectrometry and synchrotron beam lines for crystallographic studies of macromolecules encoded by the tens of thousands of genes within the human and other genomes. These advanced technologies evolved from the basic research efforts of physicists and engineers who needed these sophisticated instruments for studies of particle physics. The NIH biomedical research community, frequently in collaboration with investigators from other federal agencies, adapted the physicists' tools to study the molecular causes of disease and to develop specific therapies to prevent, cure or ameliorate the disease.

ADVANCED TECHNOLOGIES

The shared resources supported by NCRR provide a fertile environment to stimulate collaborations among investigators. Interdisciplinary research teams are indispensable as scientists begin to address more complex research problems. One example is the exploration of the human genome and the macromolecules encoded by the more than 30,000 genes identified to date within the human genome. Working at the scale of the proteome (proteins expressed by the genome), investigators may need to characterize thousands of proteins to address fundamental questions that cannot be answered by examining just one protein at a time. To assist examination of such complex problems, NCRR will initiate a program to support a system or an integrative approach for biomedical research resource centers equipped thematically with the most advanced technologies, including structural and protein purification techniques, mass spectrometry, and DNA microarrays to address the biocomplexity of research. Research teams at these centers will include investigators with wide-ranging but complementary expertise, including physicists, physical chemists, engineers, bioinformaticists, computer programmers, and both physicians and basic scientists trained in sophisticated biomedical research.

In order to respond rapidly to scientists' changing needs, NCRR works in trusted partnership with the biomedical research community and with other NIH institutes and centers. An overwhelming number of scientists we hear from have identified an urgent need for bioinformatics tools to collect, manage, analyze, and share the enormous data sets that arise from genomics, proteomics, and imaging efforts. Last year, NCRR launched an ambitious pilot

project known as the Biomedical Informatics Research Network (BIRN). BIRN is a collaborative effort with the San Diego Supercomputer Center, the National Science Foundation, and several universities. An essential feature of the BIRN testbed is the creation of infrastructure that can be deployed rapidly to other research sites throughout the country, and promises to have applications beyond neuroimaging, the project's initial focus.

Another successful pilot venture is the Internet-based network, CFnet, which NCRR established a few years ago in partnership with the Cystic Fibrosis Foundation. The initial goal of CFnet was to determine if phase 1 and 2 clinical trials could be facilitated across several GCRC sites with web-based data management. The effort proved so successful that we anticipate extending CFnet to an additional 12 GCRC sites and will include phase 3 clinical trials. NCRR, in collaboration with Internet 2, plans to establish a comparable network at the eight minority-serving medical schools to facilitate their participation in clinical trials and in studies designed to examine the factors contributing to health disparities and ways to eliminate them. This network will be extended to the entire cohort of institutions currently supported through NCRR's Research Centers in Minority Institutions program. NCRR also plans to initiate networking with a subset of academic institutions within the Institutional Development Award (IDeA) program.

GENOMICS AND GENETIC MEDICINE

NCRR supports national repositories for biologic models, which play an indispensable role in uncovering the basis of human health and disease. The genomes of animal species are remarkably similar to ours; consequently, animal models offer a wealth of information about human gene function. NCRR plans to support national resources to systematically validate, classify and characterize genetically altered animal models. National genotyping laboratories will be established to serve both the clinical research and animal model communities.

Research with embryonic stem cells may hold the key to treatment of disorders for which no effective therapies exist. These cells have the potential to develop into any type of cell in the body. To explore the full potential of these cells, NCRR will fund studies of several animal models, including nonhuman primates and rodents, to identify the factors within their microenvironments that induce embryonic stem cells to transform into insulin-producing islet cells, blood-forming cells, dopamine-producing neurons, and more---ultimately for therapeutic purposes.

Despite the fact that half of all NIH-funded research grant applications include animal-based research, relatively few veterinarians are research trained, and veterinary schools have too few faculty who can serve as mentors or role models for students. To address this need, NCRR proposes to establish academic Centers of Veterinary Research Excellence (COVRE) in colleges of veterinary medicine. The goal of COVRE is to develop a pool of research-trained veterinarians who will fill a rapidly growing need in biomedical science. COVRE will provide competitive support to further develop the research infrastructure---the research facilities, instrumentation and investigator development---of Veterinary Schools of Medicine.

RESEARCH TRAINING AND CAREER DEVELOPMENT

To address the need for research trained physicians and dentists in patient-oriented research, NCRR will expand its support for several NIH-wide career development programs. The NCRR proposes to enhance support for the Mentored Patient Oriented Research Career Development Awards (K23), and Mid-Career Investigator Awards (K24). NCRR will continue to be a major supporter of the institutional Clinical Research Curriculum Awards (K30). In FY 2001, NCRR demonstrated its commitment to the development of a cadre of clinical researchers by supporting more K23 awards than any other NIH component except one. NCRR will expand support of the loan repayment program for NCRR-supported junior investigators (dentists and physicians) who are pursuing patient-oriented clinical research career development.

NCRR proposes to expand support for clinical research pilot studies in GCRCs so that promising junior investigators and established investigators with novel ideas may collect important preliminary data to support the feasibility of research questions proposed in their research grant applications. NCRR also intends to begin funding of a new institution-based career development program for physicians and dentists. The Mentored Clinical Research Scholar Program was created as an institutional patient-oriented career development program. The program flexibly integrates educational instruction through seminars, workshops and formal courses that may lead to advanced degrees and the acquisition of biomedical research expertise in a mentored setting. Candidates must participate for a minimum of two years but not longer than five years and may be eligible for the loan repayment program. Candidates may earn an M.S., M.P.H., or Ph.D. degree in areas relevant to clinical research. The goal is to prepare physicians and dentists for independent careers in patient-oriented research.

Another NCRR effort is to enhance medical students' interest in clinical research careers through support for the Mentored Medical Student Clinical Research Program. This program provides medical and dental students with support for one year of didactic clinical investigation and mentored research at institutions with a GCRC or an RCMI Clinical Research Center. The goal is to provide support for up to 5 students per GCRC site per year. A similar program for veterinary students will be expanded.

RESEARCH CAPACITY BUILDING

NIH proposes to continue support for construction or renovation of extramural research facilities through the Research Facilities Improvement Program in FY 2003. The research community has expressed a need for Biosafety Level (BSL) 2/3/4 facilities for handling dangerous bacteria, viruses, and other agents; good manufacturing procedures (GMP) facilities for manipulation of cell therapies and production of vectors for human gene transfer. Applications from smaller institutions will be given special consideration for funding. Separately, at least $5 million of funds appropriated for construction for FY 2003 will be required to finish building a chimpanzee sanctuary system.

The NIH Institutional Development Award (IDeA) Program provides support to enhance the biomedical research capacities of institutions in states that have not fully participated in NIH research funding in the past. To develop and enhance their research infrastructure, NIH

launched two program initiatives, the Centers of Biomedical Research Excellence (COBRE) and Biomedical Research Infrastructure Networks (BRIN). In response to recommendations of institutional officials and investigators in the IDeA states and Puerto Rico, NCRR proposes to create an Internet-based network with distributed databases, using Internet 2 to link the BRINs and COBREs, to foster collaborations among the participating institutions. IDeAnet will provide access to bioinformatics tools for data analysis and visualization as well as access to scalable computing up to the teraflop level.

HEALTH DISPARITIES

Finally, in order to address health disparities, NCRR proposes to establish Comprehensive Centers for Health Disparities Research. These Centers will develop the capacity of 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. Partnerships between investigators at GCRC sites will be developed.

Mr. Chairman, the NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compared our FY 2001 results to the goals in our FY 2001performance plan.

I will be happy to respond to any questions you may have. Thank you.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Stephen E. Straus
National Center for Complementary and Alternative Medicine

on

Fiscal Year 2003 President's Budget Request
for the National Center for Complementary and Alternative Medicine

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Center for Complementary and Alternative Medicine for FY 2003, a sum of $113,823,000, which reflects an increase of $8,843,000 over the comparable Fiscal Year 2002 appropriation.

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report that compared our FY 2001 results to the goals in our FY 2001 performance plan.

FY2001 -- NCCAM's third year -- was one of exciting growth and productivity. Substantive progress was made towards advancing each of the four primary goals articulated in NCCAM's five-year strategic plan: stimulating and supporting research, research training, outreach, and facilitating integration.

BUILDING FOR SUCCESS

NCCAM's evolving success has depended on our firm adherence to a series of guiding principles. First, we solicit the best research ideas from a wide base of our stakeholders, investigators, and practitioners from the many mainstream and complementary and alternative medicine (CAM) disciplines and fields; we incorporate similarly wide perspectives into peer-review; and we invest in only the most competitive, exacting, and important work. Second, our portfolio emphasizes clinical research because CAM practices are already widely used, and the American people need information that is based on scientific evidence so that they can make informed health care choices. Third, the range of clinical conditions addressed by CAM and the cost of clinical studies, especially large trials, dictates that we leverage our intellectual and capital resources through collaboration with sister Institutes, Centers, and agencies. Fourth, CAM products and practices, in spite of their wide use, are often of variable quality. Thus, we must ensure the highest standards of safety and reproducibility of our studies.

The progress made in each of these areas has been facilitated by our creation of programs in international health research, special populations research, and clinical and regulatory affairs (PCRA), as well as the establishment of an Intramural Research Program (IRP), including the appointment of the first NCCAM Director for Clinical Research. The PCRA coordinates and monitors NCCAM-funded multi-center trials, including related Institutional Review Board (IRB) and data and safety monitoring activities. Further efforts to enhance research quality include NCCAM-funded preparation of high-priority clinical research-grade botanical products such as cranberry, Echinacea, saw palmetto, and milk thistle, for which existing supplies sold to consumers are too variable in product content and quality. The IRP creates on the NIH campus an environment for collaborative research, training, and clinical care with CAM modalities.

Evidence of our success over the past three years includes a nearly 25-fold increase in grant applications to NCCAM and a commensurate increase in the quality of our awards. Our research portfolio has begun to demonstrate the breadth and complexity typical of work supported by the more established Institutes. We have expanded our support for investigator-initiated studies on the basic mechanisms of action and clinical applications for diverse, widely used CAM therapies. NCCAM manages a substantive Centers program to investigate a range of botanical products, cancer therapies, cardiovascular disease treatments, and women's health approaches, among others, while thousands of research subjects have been enrolled into the most rigorous Phase III studies of CAM treatments ever conducted (Table). We have steadily increased the number of research training awards for pre- and postdoctoral fellows, physicians, nurses, and CAM practitioners. Our outreach efforts have benefitted from an award-winning web site and an Information Clearinghouse enriched with new fact sheets, reports, and publications for the public and the research and health care communities.

Table. Selected Randomized, Controlled Phase III Clinical Trials Supported by NCCAM

Phase III Clinical Trials	Status	Cosponsoring NIH Institutes/Centers	Target Enrollment
Shark cartilage as adjunctive therapy for **lung cancer**	Enrolling subjects	NCI	756
Ginkgo biloba to prevent **dementia**	Enrolling subjects	NIA, NHLBI, NINDS	3,000-3,500
Acupuncture for **osteoarthritis pain**	Enrolling subjects	NIAMS	570
Glucosamine/chondroitin to treat **osteoarthritis**	Enrolling subjects	NIAMS	1,588
Vitamin E/selenium to treat **prostate cancer**	Enrolling subjects	NCI	32,400
Hypericum perforatum to treat **minor depression**	Awarded	NIMH, ODS	300 (min)
EDTA chelation therapy to treat **coronary artery disease**	Under review	NHLBI	1,600 (est)
Saw palmetto/*P. africanum* to prevent progression of **benign prostatic hypertrophy**	Announced	NIDDK, ODS	3000 (est)

Allow me to highlight our approaches to and plans for some of the most complex and important facets of human health -- cancer, neurosciences, and HIV/AIDS – and international health as illustrative of our overall strategy.

CANCER

Surveys show that many cancer patients, hoping to improve their prognosis or to reduce the side effects of conventional treatments, use CAM modalities; others choose a CAM therapy as an alternative, especially for those cancers that are not responsive to conventional therapies. This widespread use has made studies of CAM approaches to cancer a high priority for NCCAM, as evidenced by a notable increase in investment in

this area. NCCAM is collaborating with the National Cancer Institute and leading cancer specialists to examine diverse complementary and alternative therapies for cancer and its complications, as palliative care treatment, and as options for care at the end of life. We jointly support CAM programs at specialized cancer centers; we co-fund the largest ever studies of the dietary supplements selenium and vitamin E for prevention of prostate cancer and shark cartilage as adjunctive therapy for lung cancer (Table). Our portfolio of recently funded studies ranges from basic molecular and pharmacological studies of herbal products used by cancer patients, to assessments of massage, spiritual approaches, and complex nutritional regimens. We hope to support additional rigorous Phase I and II studies of a variety of popular alternative treatments for which the scientific literature provides limited or no evidence to confirm their safety or effectiveness: high-dose antioxidants (e.g., vitamin C or Coenzyme Q10), herbal mixtures (e.g., Flor-Essence, Essiac, PC-SPES, or traditional Chinese medicines), single whole plant extracts (e.g., mistletoe, oleander, or green tea), biopharmacologics (e.g., MTH-68, or 714-X), or complex regimens (e.g., Revici or Gerson therapies).

THE NEUROSCIENCES

Another large component of the NCCAM research portfolio focuses on important public health needs and opportunities in the neurosciences, including studies on pain, mental health, stroke, addiction, and neurodegenerative disorders, as well as the neurobiological effects of placebos and diverse CAM therapies. Together, these studies promise to determine the range of neurological conditions for which CAM therapies may be beneficial and to further elucidate the intricate processes of the human nervous system.

Even though acupuncture has enjoyed millennia of empiric development and widespread use in Asia, it has been poorly explicated or accepted by the standards of contemporary biomedicine. Currently, NCCAM investigators are learning more about acupuncture's mechanisms of action and its value for pain relief. Several different basic science studies are applying powerful new brain imaging techniques (such as functional magnetic resonance imaging and positron emission tomography) to identify physiological linkages between needle insertion sites, ancient acupuncture meridians, and critical brain neurotransmitter and endogenous opioid pathways Many of NCCAM's studies are dedicated to investigating how effective acupuncture is at managing pain relative to other contemporary approaches. For example, in collaboration with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NCCAM will complete the largest and most rigorous trial to date of the safety and efficacy of acupuncture for the pain of osteoarthritis of the knee (Table). NCCAM supports smaller studies for other conditions including: carpal tunnel syndrome; temporomandibular disorder and postoperative dental pain; and back pain. Collectively, this is the largest ever compendium of formal acupuncture studies.

The dominant theme of research in NCCAM's IRP focuses on the body's cardinal communications network that links the mind/brain and body: neural, endocrine, and immune systems and their responses to significant age-related life stressors, such as depression, chronic pain, cognitive decline, and sleep disorders, all of which are prime targets of CAM approaches. One of the first intramural studies will examine the use of acupuncture to control nausea associated with aggressive cancer therapy.

The placebo effect also hinges on the powerful dialogue between mind and body, representing a change in a patient's condition that occurs in response to administration of otherwise inert substances or participation in a psychophysiological activity in a healing context. Research has shown that placebos affect treatment outcome. In November 2000, NCCAM, the National Institute of Diabetes and Digestive and Kidney Diseases, and 15 other Institutes, offices and health agencies cosponsored a major international conference to examine social, psychological, and neurobiological contributions to the placebo effect, and the ethical use and evaluation of placebo actions in clinical trials. In response to recommendations from the conference, NCCAM has planned and will fund, in collaboration with nine other NIH Institutes and Centers, new research initiatives aimed at elucidating the neurobiological mechanisms that mediate placebo effects, and supporting studies of social and behavioral factors that facilitate placebo responses in clinical practice settings.

HIV/AIDS

People with HIV/AIDS often incorporate CAM modalities into their treatment strategies. Consequently, NCCAM is building an innovative and broad-based research portfolio to determine the safety and efficacy of CAM modalities used by these individuals. NCCAM plans to solicit studies that build on ongoing *in vitro,* animal, and early phase clinical studies that address: the potential antiretroviral action of a number of CAM therapies either alone (e.g., dehydroepiandrosterone [DHEA]) or in concert with approved anti-HIV drugs (e.g., licorice [*Glycyrrhiza glabra*] and St. John's wort [*Hypericum perforatum*]); the amelioration of undesirable side effects of conventional treatments (including garlic to prevent the unusual deposition of fatty tissues under the skin, known as lipodystrophy); or the restoration of the immune system by dietary supplements (e.g., alpha lipoic acid or creatine). Because palliation is one of the purported benefits of many CAM therapies, NCCAM also supports several research projects on improving the quality of life for people with advanced AIDS (parallel studies are being conducted with people who have advanced cancer), including massage therapy to treat depression and improve the quality of life, cognitive behavioral coping and Tai Chi to reduce stress, and the role spirituality plays in sustaining one's will to live.

INTERNATIONAL HEALTH RESEARCH

Recognizing that a global CAM research network would also enhance CAM research activities in the United States by affording investigators access to unique

bioresources and traditional therapies, NCCAM established a research program on international health in FY 2001. The goal is to promote the validation of indigenous CAM practices by encouraging their rigorous assessment in their native context in a culturally sensitive manner. Collaborations with the Fogarty International Center, the World Health Organization, and other agencies are facilitating these endeavors. In accord with the strategic plan for this effort, NCCAM has begun by convening international workshops and plans to solicit applications to develop an international site of CAM research excellence.

CONCLUSION

While many CAM remedies have been employed for centuries, we still have much to learn about them. By continuing our studies on their underlying mechanisms and clinical effects, we will discern which approaches are safe and effective, and therefore suitable for incorporation into medical practice, while well-informed consumers will reject those that are not.

I am now happy to take your questions about NCCAM's activities and plans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. John Ruffin
National Center on Minority Health and Health Disparities

on

Fiscal Year 2003 President's Budget Request
for the National Center on Minority Health and Health Disparities

Mr. Chairman and Members of the Committee:

I am honored to appear before you as the Director of the National Center on Minority Health and Health Disparities (NCMHD) to present the President's budget request for FY 2003, a sum of $187.159 million, which reflects an increase of $29.294 million over the comparable FY 2002 appropriation. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compares our FY 2001 results to the goals in our FY 2001 performance plan. As performance trends on research outcomes emerge, the GPRA data will help NIH to identify strategies and objectives to continuously improve its programs.

Thanks to the support of the Congress, the National Center on Minority Health and Health Disparities was created in January 2001, as mandated by Public Law 106-525. NCMHD's mission is to lead, coordinate, support, and assess the NIH effort to reduce and ultimately eliminate health disparities. The Center will achieve its mission by conducting and supporting basic, clinical, social, and behavioral research, promoting research infrastructure and training, fostering emerging programs, disseminating information, and reaching out to minority and other health disparity communities. NCMHD envisions an America in which all populations will have an equal opportunity to live long, healthy and productive lives.

Over the past year, NCMHD has worked diligently with its partners, the other Institutes and Centers (ICs) and Offices at NIH, to implement its statutory requirements. I am grateful for the extensive support and cooperation that the Center has received from Dr. Ruth Kirschstein, Acting Director of NIH, and all of the other IC Directors. The help of the other ICs is demonstrated in the Center's achievements that I will discuss today. Last year, I informed you of what we were planning to attain. Now, one year later, I am proud to share with you highlights of what we have accomplished. The Center has successfully developed its organizational structure and continues to hire new staff to carry out its programs and initiatives.

NIH COMPREHENSIVE STRATEGIC PLAN AND BUDGET

For the first time in the history of the National Institutes of Health, it will have a comprehensive Strategic Plan and Budget that will be a guiding mechanism for the conduct and support of all NIH minority health disparities research and other health disparities research activities. NCMHD was honored to be charged with the development of this plan in collaboration with the Director of NIH and the Directors of the other NIH ICs. The Center has submitted the Strategic Plan and Budget to the Office of the Director, NIH, for review.

The Plan was developed with substantial input from various stakeholders including the public, academia and health professionals representing those who disproportionately experience disparities in health. It describes current activities and future plans of the NIH to address the health disparities crisis, to build a culturally competent cadre of biomedical and behavioral investigators and to increase the number of minority clinical and basic medical scientists who are essential to the success of our efforts. There are three main goals of the plan--research, research infrastructure and community outreach which encompasses information dissemination and public health education. Within each goal there are areas of emphasis and objectives to accomplish the priorities identified or mandated. Each objective outlines an action plan, time-line, performance measures to monitor and report progress and outcome measures to demonstrate accomplishment and ultimate impact. The Plan will continue to be an evolving document over the next five years. Once finalized, it will be posted on the NCMHD website at www.ncmhd.nih.gov on a continuing basis, and comments from the public will be welcomed at any time. We will update and revise the Strategic Plan and Budget annually with the continued collaborative input of the other NIH ICs, and we will provide annual reports on our progress.

NCMHD CONGRESSIONALLY MANDATED PROGRAMS

NCMHD also has made rapid progress in implementing its three major congressionally mandated programs --the Loan Repayment Program, the Endowment Program for Section 736 (PHS Act) institutions, and the Centers of Excellence Program. Currently, we are in the preliminary phase of implementing the Centers of Excellence Program, which we have named Project EXPORT, "Centers of EXcellence in Partnerships for Community Outreach, Research on Health Disparities, and Training." We are grateful to the NIH ICs for providing us with the necessary mechanisms and support which made it possible for the NCMHD to launch in fiscal year 2001 our two new loan repayment programs and the Endowment Program for Section 736 institutions.

THE LOAN REPAYMENT PROGRAMS

In FY 2001, the Center established the Loan Repayment Program for Health Disparities Research, mandated in law, and the Extramural Clinical Research Loan Repayment Program for individuals from disadvantaged backgrounds, the authority for

which was delegated to the Center by the Acting Director of NIH. The Loan Repayment Program for Health Disparities Research is aimed at increasing the number of highly qualified health professionals in health disparity research careers, and focuses on basic, clinical, and behavioral research with priority given to biomedical research. The Extramural Clinical Research Program seeks to increase the number of highly qualified health professionals from disadvantaged backgrounds who pursue clinical research careers. Applicants to the loan repayment programs, must have a health professions degree, such as a M.D., Ph.D., D.O., D.D.S., or equivalent doctorate degree. Individuals completing their residencies, post-doctoral training, and internships may also apply.

We are pleased to report that the first round of loan repayment awards were made to 45 health professionals in FY 2001, eight months after the Center's creation. Twenty eight awards went to the Health Disparities Research Loan Repayment Program, and seventeen awards to the Extramural Clinical Research Loan Repayment Program. A total of 125 applications were received. Based on the tremendous interest in the program, during the current fiscal year we anticipate receiving about 350 applications. We plan to announce the FY 2002 awards in September.

THE ENDOWMENT PROGRAM

The Center is fortunate to have had similar success in implementing the Endowment Program for Section 736 Institutions, as required by Public Law 106-525. These institutions are Centers of Excellence already established by the Health Resources and Services Administration (HRSA) under Section 736 of the Public Health Service Act. The purpose of this program is to facilitate capacity building for minority health disparities research and other health disparities research at institutions that have a demonstrated commitment to educating and training researchers from minority and health disparity populations. In FY 2001, the NCMHD made the first round of endowment awards to five institutions. The Center will continue its commitment to the Endowment Program this year. The preliminary phase of the application process will begin with the release of the next RFA in April to culminate with the issuing of FY 2002 awards in September.

CENTERS OF EXCELLENCE PROGRAM

Our efforts to implement our Project EXPORT Centers of Excellence Program are well underway. The purpose of the Project EXPORT program is to develop and implement a network of centers of excellence at academic institutions with a significant number of students from racial and ethnic minority and other health disparity populations. This program aims to promote the conduct of minority health and/or health disparity research aimed at reducing disparities in health status; promote the participation of members of health disparity groups in biomedical and behavioral research, prevention and intervention activities through education and training; and build research capacity in minority serving institutions. The RFAs for the program have been released, and the Center is currently accepting applications through May 24. We have

just successfully completed a series of four technical assistance workshops across the country, which provided the community with guidance on all aspects of completing and submitting applications for the program. The attendance and level of participation at the workshops was outstanding, and we look forward to receiving a number of highly competitive applications. We expect to announce the FY 2002 awards in September.

NEW INITIATIVES

NCMHD is excited about the opportunity to undertake new approaches to the health disparities crisis. The Center is presently exploring the development of the following additional programs for FY 2003:

1) The Virtual University Program: to improve training outcomes for students from minority and other health disparity groups, improve the transition from undergraduate to graduate programs and to independent investigators, and serve as a resource for continuing education and/or retooling for faculty at minority serving institutions.

2) The Rural Poor and other Health Disparity Groups: NCMHD will collaborate with the National Institute on Dental and Craniofacial Research (NIDCR) to support 1) planning grants for research to prevent or reduce oral health disparities, 2) pilot grants for research to prevent or reduce oral health disparities, and 3) research infrastructure and capacity building for minority institutions to reduce oral health disparities.

3) Community Outreach: the NCMHD is committed to creating communication channels that lend themselves to the bi-directional, interactive nature of effective outreach. Accordingly, the NCMHD will divide its outreach efforts into three major objectives: 1) Outreach to Communities and their Community Based Organizations 2) Outreach to Health and Social Service Professionals 3) Outreach to Health, Research and Social Service Institutions, Professional Organizations, and the Business Sector.

4) Mississippi Delta Project: with a medical research agenda for the Mississippi Delta Region, the NCMHD will concentrate on (1) solidifying the organizational and technological network within the community to conduct research on health disparities; (2) increasing the level of involvement of community residents in the health research; (3) facilitating the availability of culturally-appropriate health education material; and (4) establishing a base for involvement of small businesses with these entities.

CONCLUSION

The NCMHD is grateful to the Congress, the Administration and the NIH Institutes and Centers for the overwhelming support that each has provided the Center in transitioning from the Office of Research on Minority Health, to the National Center on Minority Health and Health Disparities. I am proud of the progress that the Center has made over the past year in establishing its organizational structure and programs. The

American people can now learn about the Center's activities and programs by accessing our new website at www.ncmhd.nih.gov which is now averaging about 50,000 hits a month. Through continued and increasing collaborative ventures, NCMHD will work diligently to define the health disparity issue for every American, and garner their support to someday ensure an America in which all populations will have an equal opportunity to live long, healthy and productive lives.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Gerald T. Keusch
John E. Fogarty International Center

on

Fiscal Year 2003 President's Budget Request
for the John E. Fogarty International Center

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the Fogarty International Center for FY 2003, a sum of $63,833,000 which reflects an increase of $6,480,000 over the comparable FY 2002 appropriation.

SCIENCE FOR GLOBAL HEALTH

For 34 years now, the Fogarty International Center (FIC) has built alliances for global health to advance medical research for the benefit of all. We live in an interconnected, international community and because science is an inherently international endeavor, FIC initiatives reach across borders and contribute knowledge to enhance health here at home while narrowing the gap in health status between rich and poor countries.

We face many global health challenges and threats. The World Health Organization (WHO) estimates that 1,200 people die each hour from an infectious disease. AIDS has killed more than 22 million people, leaving in its wake households without bread-winners, orphaned children, and unspeakable human suffering. In the U.S., 45,000 people become infected each year. As we battle AIDS, TB, malaria and other infectious diseases on the rise around the globe, we confront new microbial threats and drug-resistant strains of common foes. At the same time, we know that chronic diseases will become more important causes of the global burden of disease in the coming decades (WHO/World Bank Report, 1996). With aging of populations and changing demographics, due to new economic growth, heart disease, stroke, diabetes, mental illness and other chronic diseases, will all add to the increasing health burden on the global community. As we combat today's diseases challenges, we must prepare for those on the horizon. Sound science is at the foundation of our approach to addressing these global health threats.

As a nation, our interest in global health stems not only from our humanitarian concerns as we work to alleviate human suffering, but also from an enlightened self-interest. Traditionally, such interests focus on protecting our nation from imported diseases. Now we recognize the political and economic benefits as well: healthy, stable countries make strong allies and trading partners. Yet, our self-interest goes beyond these issues. Through partnerships with scientists from around the world, including those

in developing countries, we are able to identify new strategies and new understandings of disease processes, including for AIDS, TB, and chronic diseases such as heart disease, that affect us all. In light of the tragic events of September 11th, these partnerships take on new meaning. As President Bush noted to the U.N. General Assembly soon after the tragedy, "My country is pledged to investing in education and combating AIDS and other infectious diseases around the world. Following September 11th, these pledges are even more important. In our struggle against ... poverty and despair, we must offer an alternative of opportunity and hope." The programs of the FIC provide both scientific opportunity and hope for generations of scientific leaders, especially those in the poorest, most marginalized parts of the world.

NARROWING THE KNOWLEDGE GAP

FIC currently addresses global health challenges through twenty research and research capacity building programs as well as through its leadership of global scientific alliances. Working in over 100 countries and through more than 120 U.S. universities, medical schools and schools of public health, FIC-supported scientists are in the vanguard in advancing research and in training the next generation of scientists. The pairing of research with research training is the cornerstone of FIC's approach toward building capacity in the developing world, and it has produced over time spectacular and enduring results. A complete description of the FIC Strategic Plan is available on the Web at http://www.nih.gov/fic/about/plan.html.

FIC's AIDS International Training and Research Program, now in its 14th year, has provided Ph.D.-level, Master's-level and advanced short course training to thousands of scientists in the developing world. Research successes supported through that program include identification of effective strategies to reduce HIV transmission from mother to child, insights into risk behavior that leads to HIV infection and related intervention strategies, and development of technologies to ensure the safety of the blood supply. Importantly, scientists who received training through the AIDS program are competitive for other NIH funds, as well as funds from other science agencies, and become the leaders in science in their home countries as new studies and clinical interventions are developed and tested.

Among the outstanding leaders associated with FIC's research capacity building programs is Dr. Nelson Sewankambo, a long-standing FIC affiliate of our AIDS program, now Dean of the School of Medicine in Kampala, Uganda. Dr. Crispus Kiyonga, Minister of Health of Uganda, has received advanced training in AIDS research methodologies with FIC support to Johns Hopkins University. Both individuals had a major impact on the formulation and implementation of AIDS policies that have contributed to the decline in overall HIV infections in Uganda. Today, Dr. Kiyonga leads the United Nations Global Fund for AIDS, TB and Malaria, a newly-established fund to address the burden of those diseases in the developing world. In addition, Dr. Phillippa Musoke, once a trainee in the AIDS program, later competed successfully for NIH funds and went on to make one of the seminal discoveries in Uganda on the use of anti-retroviral drugs to block mother to child transmission of AIDS. Looking more broadly at the impact of the AIDS program on individual career development and scientific productivity, a review of the presentations at the most recent AIDS International

Conference held in Durban, South Africa, in June 2000 shows that fully 25 percent of all research papers were authored or co-authored by FIC-supported scientists from developing countries. Ultimately it is people who drive progress.

Using the same capacity building paradigm as with AIDS, FIC supports research and research training in other critical areas of global health concern, including in the fields of maternal and child health, environmental and occupational health, and tobacco and health, while building essential capacity in ethics and information technology. While training the next generation of researchers, key advances in critical areas have emerged: a U.S.-Peru team developed a low-cost diagnostic test for multi-drug resistant TB that is fast, cost-effective and can be used in resource-poor settings; a U.S.- Brazil team tracked the spread of penicillin resistance in populations; a U.S.- China team elucidated the risks associated with unsafe blood products and the spread of HIV; and a U.S.- Russia team defined intravenous drug use and sexual practices related to the burgeoning AIDS epidemic in Russia to identify effective interventions. As a companion to these research capacity building programs for developing country scientists, FIC supports a career development program for junior U.S. scientists to allow them opportunities to conduct research on global health issues in developing country institutions.

FIC's support for research also includes work that spans diverse disciplines to generate new knowledge. For example, the International Cooperative Biodiversity Groups program, launched in 1993, fosters drug development from diverse plants and microorganisms. At the same time, working through community groups and local governments, it works to conserve biodiversity and promote economic development where these source organisms are located. A number of novel lead compounds to combat a range of diseases, including AIDS, TB, malaria, leischmaniasis, bacterial infections, and cancer, are now in animal testing programs in collaboration with pharmaceutical partners. Additionally, FIC is working to strengthen the knowledge base of the linkage between health status and economic development through joint awards to economists and health scientists. Launched with other NIH partners and the World Bank, this new FIC program supports studies to promote collaborative decision making among Ministries of Development, Finance and Health in the developing world, for example studies that document the link between the nutritional status of children and adult economic productivity, providing the evidence base for appropriate interventions.

GLOBAL LEADERSHIP

As a leader in the global health arena, FIC initiates partnerships and implements research and training with other NIH components on issues of common interest as well as with other U.S. agencies, science funding agencies abroad, international organizations, foundations and other non-governmental groups. FIC is the Secretariat for the Multilateral Initiative on Malaria (MIM), a global alliance of organizations and institutions committed to advancing malaria research and building research capacity in the developing world. FIC works closely with the National Institute of Allergy and Infectious Diseases, the National Library of Medicine, the WHO and science funding agencies in France, the United Kingdom, and other countries to advance the goals of the MIM. In addition to its support for collaborative research projects and training in

malaria, the Secretariat will hold the third Pan-African and International Malaria Conference in Arusha, Tanzania in November 2002. Other examples of FIC's leadership in key global health areas include a major project to develop a new assessment of "Disease Control Priorities in Developing Countries," in partnership with the World Bank, WHO, and the Bill and Melinda Gates Foundation. This new initiative will develop data on disease burden and health care infrastructures in the developing world as a means to inform policy makers. FIC has been selected by the partners as the Secretariat for the Project. In another area, FIC is playing a leading role in advising on the development of the Global Alliance for Improving Nutrition, a public-private sector partnership to enhance global health through food fortification and other nutritional interventions.

MEETING UNMET GLOBAL HEALTH NEEDS: FY 2003 INITIATIVES

Translating AIDS and TB advances from bench to bedside in the developing world: As the global community continues to work to address the paired pandemics of AIDS and TB, donations of anti-AIDS drugs, increased funding from foundations and other circumstances make it possible to consider more aggressive care for those already infected while working to prevent new infections. As countries in the developing world gear up to test new treatment protocols, the need for enhanced clinical research skills and support becomes more and more important. Building on the foundation that FIC and its partners have established over many years, FIC has spearheaded the development of a new program to expand training in AIDS and TB to include clinical, operational and health services research. This program, developed closely with NIH partners as well as with other U.S. agencies and non-governmental groups, will build the capacity in poor countries so that research advances made at the bench may be rapidly translated into the delivery of health care for those who are in greatest need.

Combating Brain Drain from Developing Countries: As we work to address global health challenges, ensuring that scientists from the developing world who train in the U.S. have opportunities to conduct research on their return home is increasingly critical. To foster their productive "re-entry," FIC and partners at NIH will expand the pilot effort to provide competitive awards to junior scientists from the developing world who have "graduated" from FIC training programs in U.S. universities or who have received training in the NIH intramural laboratories in Bethesda. This program encourages continuity of the scientist-to-scientist collaboration, builds capacity in global health areas in the developing world, and encourages junior scientists from the developing world to return home because they can establish independent research careers, and builds relationships between our nations.

Addressing the Growing Burden of Brain Disorders: Mental illness and brain disorders will contribute increasingly to the global burden of disease in the coming decades (Institute of Medicine Report on Neurological, Psychiatric and Developmental Disorders, 2001). In addition to the human suffering associated with these conditions, they contribute to significant losses in economic productivity. FIC will work with partners across NIH to address the challenges of neurological, psychiatric, and developmental disorders in the developing world. In FY 2003, FIC will launch a program to build research capacity in the field of brain disorders while supporting

operational research to identify and implement interventions that are relevant, feasible and affordable in low-resource settings. It is expected that the benefits of this program will be realized not only in the developing world but also in the U.S., for populations that share genetic and cultural similarities with those in resource-poor settings abroad.

The Linkages between Health, Environment, and Economic Development: Understanding the linkages between sustainable development, environmental change and health is a great challenge to those who set national health policy, especially in resource-limited nations. Building on current FIC research programs that address the impact of improving health on economic productivity on the one hand, and research to understand the impact of environmental degradation on the other, FIC will launch a new program to more fully understand the relationships between health, environment, and economic development. This research program will focus on the effects of urbanization in low-resource countries, the health effects and consequences of agricultural practices, water-borne diseases, nutrition and food safety, and the economic, social and health costs and benefits of globalization.

Stigma and Global Health: One of the pervasive problems affecting health globally is the stigma attached to certain diseases and its powerful impact on individuals, families and communities. Stigma inhibits individuals from obtaining diagnostic services or care, and from participating in research studies designed to find solutions to their condition, and results in ostracism, physical harm or even death. As the prevalence of stigmatizing conditions, including AIDS, mental illness, drug use and others, increases in the coming decades, the impact of stigma will also increase. Building on the out-comes of the FIC-led "International Conference on Stigma: Setting a Research Agenda" held in September 2001, FIC and partners across NIH will launch a new research and training program to enhance our understanding of the social and cultural determinants of stigma, both in the United States and in the developing world, and the behavioral responses resulting from stigmatization in different cultural settings. This understanding is fundamental to the identification and testing of effective behavioral interventions.

Trauma and Injury – New Challenges: Every day the global toll from trauma and injury from all causes is almost 16,000 deaths, and far greater numbers incur permanent disability (WHO Report; 1999). In the coming decades, road traffic accidents, injuries and trauma will contribute increasingly to the global burden of disease. FIC and NIH partners are working to address this challenge through the development of a multi-disciplinary program to link basic research on trauma, burns, wound-healing, post-traumatic stress disorders and other conditions with training for scientists from the developing world. One objective is to develop low-cost effective interventions that would be applicable in the developing world as well as within the developed world.

CONCLUSION

As we enter the 21st century, the health challenges facing the U.S. and the global community will continue to converge. With strong scientific partnerships across national borders, we are positioned to tackle shared health problems and to develop shared solutions. The programs of the FIC are critical to building these partnerships and to advancing medical research for the benefit of all the world's people.

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report, which compared our FY 2001 results to the goals in our FY 2001 performance plan.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Yvonne T. Maddox
Acting Deputy Director, National Institutes of Health

on

FY 2003 President's Budget Request
for the Office of the Director

Mr. Chairmen, Members of the Committee:

I am pleased to present the President's budget request for the Office of the Director (OD) for FY 2003, a sum of $258,544,000 which reflects an increase of $19,720,000 over the comparable FY 2002 appropriation. The OD provides leadership, coordination, and guidance in the formulation of policy and procedures related to biomedical research and research training programs. The OD also is responsible for a number of special programs and for management of centralized support services to the operations of the entire NIH.

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

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

THE OFFICE OF AIDS RESEARCH

In response to the AIDS pandemic, NIH has developed a comprehensive biomedical and behavioral research program to better understand the basic biology of HIV, develop effective therapies to treat it, and design interventions to prevent new infections from occurring. The role of the Office of AIDS Research (OAR) is to plan and coordinate this research program that is

sponsored by 25 NIH Institutes and Centers (IC's); to serve as a focal point for AIDS policy and budget development; and to monitor and foster plans for NIH involvement in international AIDS research activities.

The OAR develops an annual comprehensive AIDS research plan and budget, based on the most compelling scientific priorities that will lead to better therapies and prevention for HIV infection and AIDS. Those priorities are determined through a unique and collaborative process involving the NIH institutes and non-government experts from academia and industry, with the full participation of AIDS community representatives. The plan is divided into five Scientific Areas of Emphasis and four Areas of Special Interest. The plan serves as a framework for developing the NIH AIDS budget, for determining the use of NIH AIDS-designated dollars, and for tracking and monitoring those expenditures. The FY 2003 budget request for OAR is $58.3 million.

THE OFFICE OF RESEARCH ON WOMEN'S HEALTH

The Office of Research on Women's Health (ORWH) is the focal point for women's health research at NIH and strives to ensure that research supported by NIH addresses the health concerns of women, that women are appropriately included as subjects in clinical research, and that women are encouraged to pursue and succeed in careers in biomedical research.

The priorities for research and the science-based initiatives of ORWH are based on the recommendations in the report of the Task Force on the NIH Women's Health Research Agenda for the 21st Century, "An Agenda for Research on Women's Health for the 21st Century" with consideration of new advances in science and continuing gaps in knowledge. ORWH will strive to address these scientific initiatives about women's health and sex and gender factors in disease. In FY 2003, the OD budget request of $40.7 million includes an increase of $3.3 million over the FY 2002 enacted budget of $37.3 million for ORWH to implement recommendations within this agenda, including the prevention and detection of ovarian and cervical cancer, new and emerging issues surrounding the inclusion of women in clinical studies, successful aging and health-related quality of life issues, sex and gender differences in health and disease, developing an initiative with OAR to address priorities for prevention, care, treatment, and support for girls and women with HIV/AIDS, research regarding women and eye disease, and reproductive health including the full range of gynecologic and obstetrical conditions, fibroids, and the menopausal transition.

ORWH will support centers for research and career development including a cadre of interdisciplinary researchers doing women's health research. ORWH, NIH IC's, and the Agency for Healthcare Research and Quality will support career development programs that promote the pursuit of interdisciplinary research careers relevant to women's health and encourage basic and clinical research careers. ORWH will also encourage networks of interdisciplinary researchers by providing opportunities for them to meet yearly and exchange ideas and experiences at NIH. In addition, ORWH and the NIH IC'S will support Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health to study and advance interdisciplinary research to better understand the basic molecular, cellular, and physiologic mechanisms underlying the response of both women and men to therapeutic interventions and hormonal factors. Finally,

ORWH will continue to work with OER and OIR to monitor compliance with and facilitate analysis by gender of the policies for the inclusion of women and minorities in clinical research.

THE OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

NIH has become increasingly aware of the importance of the contributions from behavioral and social sciences research to improving the health of the population. The Office of Behavioral and Social Sciences Research (OBSSR) provides leadership within the NIH community 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 FY 2003 OD budget includes $25.8 million for OBSSR, an increase of over $2 million or 9 percent above the FY 2002 appropriation.

In its efforts to increase support for behavioral and social sciences research, OBSSR frequently identifies important topics that have relevance across many NIH IC's. One such initiative that OBSSR is developing is in the area of environmental influences on gene expression. The dramatic advances in genetic research in the recent past have only served to underscore that health outcomes are a result of interplay between genetic make-up and environmental influences. While the human genome has been characterized, the environment is less well understood. OBSSR, in collaboration with several Institutes, is undertaking an initiative to improve the understanding of the key environmental factors that affect gene expression and health.

While the results of many behavioral and social science studies hold great promise for improving health, the incorporation of those results into health care is often slow or nonexistent. OBSSR is joining with several NIH Institutes to explore opportunities to work with the Centers for Disease Control and Prevention and the Agency for Healthcare Research and Quality to improve the translation of evidence-based behavioral and social interventions into health care.

Many of the most exciting scientific developments are occurring at the intersection of behavioral and social science research and biomedical research. OBSSR and several IC's are in the process of developing new approaches to training individuals to be prepared to undertake a program of research that extends well beyond traditional disciplinary boundaries.

THE OFFICE OF DISEASE PREVENTION

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 FY 2003, the Office of Dietary Supplements (ODS) within ODP will continue to promote the scientific study of the use of dietary supplements. The Office will continue to support investigator-initiated research through the Research Enhancement Awards Program (REAP) and through program announcements with other IC's at NIH. The Office will also stimulate research through conduct of conferences, workshops, and presentations at national and

international meetings. In continuing efforts to inform the public about the benefits and risks of dietary supplements, the ODS expanded the International Bibliographic Information on Dietary Supplements database to include a consumer-oriented search strategy. ODS is nearing completion of public-oriented information pages (Fact Sheets) about specific vitamin and mineral dietary supplements for wide dissemination in print and on the Internet. These are to be followed by a series of Fact Sheets for botanical and herbal supplements, which are being developed in conjunction with the National Center for Complementary and Alternative Medicine. The FY2003 budget request for ODS is $18.5 million.

In FY 2002, ODS will commission an evidence-based review on the relationship between omega-3 fatty acids and coronary heart disease. A report of the review, done in collaboration with the National Institute of Heart Lung and Blood Institute and other NIH IC's, will be available in FY 2003. The results of the report will serve as the basis for planning an NIH research agenda on omega-3 fatty acids. To determine the efficacy and safety of dietary supplements containing ephedra, ODS with other Federal partners, commissioned an evidence-based review of ephedra efficacy and safety. This report is currently being drafted and will be available late summer, 2002. ODS has also nominated ephedra for study by the National Toxicology Program of the National Institute of Environmental Health Sciences.

Congressional language in the FY 2002 appropriation report has directed ODS to enhance an ongoing collaboration for the development, validation, and dissemination of analytical methods and reference materials for botanical dietary supplements. ODS will work with other Federal partners, non-governmental organizations, industry, and academia to meet this objective. In February 2002, ODS held a public stakeholder's meeting to receive comment on the development and validation of analytical methods and reference materials for dietary supplement products.

Another component of ODP, the Office of Rare Diseases (ORD), develops and disseminates information to patients and their families, health care providers, patient support groups, and others and forges links among investigators with ongoing research activities in this area. The ORD continues to support workshops and symposia to stimulate research and to identify research opportunities related to rare diseases. To provide better and faster information, ORD, together with the National Human Genome Research Institute (NHGRI), established the Genetic and Rare Diseases Information Center to respond to requests for information about genetic and rare disorders. The FY 2003 budget request for ORD is $11.3 million.

The ORD is also planning to respond to the critical needs of patients with rare, life threatening diseases by establishing regional and intramural centers of excellence. These centers will support rare diseases research and diagnostic research that will eventually benefit many of those patients whose diagnoses have been elusive despite extensive prior efforts to determine the exact nature of their illnesses.

THE OFFICE OF SCIENCE EDUCATION

The Office of Science Education (OSE) plans, develops, and coordinates a comprehensive science education program 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 develops, supports, and directs new program initiatives at all levels with special emphasis on targeting students in grades kindergarten to 12, their educators and parents, and the general public. It maintains a website as a central source of information about NIH science education resources, establishes national model programs in public science education, such as the NIH Mini-Med School, and promotes science education reform as outlined in the National Science Education Standards and related guidelines. OSE works closely with the NIH extramural, intramural, women's health, laboratory animal research, and minority program offices on science education special issues and programs to ensure coordination of NIH efforts.

Begun in FY 1997 as a major new initiative in collaboration with the NIH institutes and centers, the Office of Science Education (OSE) develops and distributes standards-based curriculum supplements for use in K–12 classrooms. These supplements are distributed free-of-charge to science teachers and school administrators throughout the U.S., and are designed to complement existing life science curricula that are used at the state and local levels. The NIH Curriculum Supplements align with the *National Science Education Standards*; incorporate inquiry-based learning activities; promote peer collaboration, problem solving, and critical thinking skills; and include cutting-edge science and up-to-date medical research findings that are translated into real-world scenarios.

As of summer 2001, over 40,000 copies of the first three titles in the series (*Cell Biology and Cancer, Emerging and Reemerging Infectious Diseases, and Human Genetic Variation*) have been distributed to teachers across the nation. This represents a potential audience of more than 1.5 million high school students. Preliminary evaluation research of the effectiveness of the curriculum supplements conducted in New York City has yielded promising results. Students' ratings of how well the material covered was connected to their lives were 96% higher in classrooms using the NIH Curriculum Supplements. Students using the NIH Curriculum Supplements also out-performed their peers on a standardized test of science achievement.

LOAN REPAYMENT AND SCHOLARSHIP PROGRAM

The NIH, through the OIR maintains the Loan Repayment and Scholarship Program (LRSP). The LRSP supports the following programs: the Clinical Research Loan Repayment Program for the repayment of the educational debt of awardees if they agree to conduct clinical research as NIH employees; the Undergraduate Scholarship Program in which scholars agree to serve as NIH employees after graduation, one year for each year of scholarship support received; and the General Research Loan Repayment Program which provides support for physicians and scientists engaged in both basic and clinical research activities at the NIH. Technical and logistical support is also provided for two extramural loan repayment programs funded with the IC's.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Donald A.B. Lindberg
National Library of Medicine

on

Fiscal Year 2003 President's Budget Request
for the National Library of Medicine

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 2003, a sum of $315,163,000, which reflects an increase of $33,411,000 over the comparable Fiscal Year 2002 appropriation.

It is a phenomenon that has challenged the NLM and changed the way we operate: the ability to freely and instantaneously provide access via the Internet to the information we have accumulated for decades. MEDLINE, our database of more than 11 million references and abstracts to medical journal articles is now being searched 400 million times a year. MEDLINEplus, our extensive information resource for the general public, is viewed 100 million times a year. This activity dwarfs previous usage of the NLM's bibliographic services, whether electronic or print. It has changed fundamentally how the Library operates: how and what it collects, how it preserves information, and how it disseminates biomedical knowledge.

The consequence of this communications revolution is most easily seen in the greatly expanded user community we serve. This community includes not only traditional audiences—health professionals, scientists, educators, students, and librarians—but now, also, for the first time, the general public. Surveys of Internet usage show that health information is one of the most cited reasons for searching the Internet, and we estimate that fully one-third of MEDLINE searching (and almost all of MEDLINEplus usage) is by the public. We believe that the trend toward virtual ubiquity in electronic information access will accelerate and that the NLM must be able to move quickly to ensure that those who need reliable health information have access to it. The effort to double the NIH budget, which is fulfilled in the FY 2002 President's Budget request, makes this a realistic goal for the Library.

An example of NLM's ability to respond rapidly to changing circumstances was its action in putting up on its Web site information about bioterrorism and biowarfare, including extensive information about anthrax and smallpox. NLM information specialists, both medical librarians and specialists in toxicology information, reviewed existing resources and quickly made reliable data available to all. In fact, in the weeks following September 11, more people looked at anthrax information on MEDLINEplus than looked at cancer information.

Despite the NLM's extensive involvement with computer and communications technology, the staff is ever mindful of its responsibility to maintain the integrity of the world's largest collection of medical books and journals. Increasingly, this information is in digital form, and the NLM, as a national library responsible for preserving the scholarly record of biomedicine, is working with the Library of Congress and others to

develop a strategy for selecting, organizing, and ensuring permanent access to digital information. Regardless of the format in which the materials are received, ensuring their availability for future generations remains the Library's highest priority.

SERVING SCIENTISTS AND THE HEALTH PROFESSIONS

From the fledgling database first mounted in 1971, usable only by trained librarians, MEDLINE has grown into the world's largest bibliographic database of biomedical literature. Anyone with access to the World Wide Web can easily search it. Some 4,600 journals published around the world are currently indexed for MEDLINE. The Library is also converting information from the 1950s into MEDLINE form, so that valuable research information on smallpox and tuberculosis, to take just two pertinent examples, will be available to today's scientists and health professionals.

The sophisticated yet easy-to-use access system for searching MEDLINE on the Web is called PubMed. Since its introduction in 1997, continual improvements have been made, and today PubMed offers a high degree of flexibility to users. For example, it now has links to half of the journals in MEDLINE, permitting access to the full text of articles referenced in the database. Where such links are not available, users may avail themselves of the PubMed feature known as "Loansome Doc" to order an article directly from a library in the National Network of Libraries of Medicine.

A new service to the scientific community is PubMedCentral. This Web-based digital archive of life sciences journal literature was created by NLM's National Center for Biotechnology Information. Publishers electronically send peer-reviewed articles be included in PubMedCentral. A journal may deposit material as soon as it is published, or it may delay release for a specified period of time. NLM guarantees free access to the material; copyright remains with the publisher or the author. There are at present a dozen journals in PubMedCentral, with more soon to come online.

The National Center for Biotechnology Information (NCBI) designs and develops databases to store genomic sequence information and creates automated systems for managing and analyzing knowledge about molecular biology and genetics. With the release of the "working draft" of the human genome in 2001, the global research focus is turning from analysis of specific genes or gene regions to whole genomes, which refers to all of the genes found in cells and tissues. To accommodate this shift in research focus, NCBI has developed a suite of resources to support the comprehensive analysis of the human genome and is thus a key component of the NIH Human Genome Project. NCBI is responsible for all phases of the NIH GenBank database, a collection of all known DNA sequences. GenBank is growing rapidly with contributions received from scientists around the world and now contains more than 13 million sequences and is accessed by 50,000 researchers each day.

Scientists use not only the sequence data stored in GenBank, but avail themselves of the sophisticated computational tools developed by NCBI investigators, such as the BLAST suite of programs for conducting comparative sequence analysis. Entrez is NCBI's integrated database search and retrieval system. It allows users to search enormous amounts of sequence and literature information with techniques that are fast and easy to use. Using this system, one can access NCBI's nucleotide, protein, mapping, taxonomy, genome, structure, and population studies databases, as well as PubMed, the retrieval system for biomedical literature. NCBI's Map Viewer provides graphical displays of features on NCBI's assembly of human genomic sequence data as well as cytogenetic, genetic, physical, and radiation hybrid maps. The public "Human Gene Map" is another example of an important analysis tool developed by NCBI researchers.

GeneMap represents an outline of the draft human genome and contains the location of more than 35,000—about half—of all human genes.

SERVING THE PUBLIC

There was an unexpected consequence of making MEDLINE freely available on the Web in 1997: what had been a scientific information resource used almost exclusively by medical librarians, scientists, and health professionals was discovered by consumers. NLM estimates that 30 percent of all MEDLINE searching is being done by the public. In an effort to arm the public with more useful information, the NLM, in 1998, introduced MEDLINEplus, a source of authoritative, full-text health information from the NIH institutes and a variety of non-Federal sources.

MEDLINEplus has grown tremendously in its coverage of health and its usage by the public. There were one million unique users in January 2002. The original two dozen "health topics," containing detailed consumer information on various diseases and health conditions, have been increased to more than 550. Other information available through MEDLINEplus includes medical dictionaries, an extensive medical encyclopedia written in lay language with thousands of illustrations, detailed information about more than 9,000 brand name and generic prescription and over-the-counter drugs, information in Spanish, directories of health professionals and hospitals, and links to organizations and libraries that provide health information for the public. The most recent additions to MEDLINEplus are illustrated interactive patient tutorials and a daily news feed from the public media on health-related topics. To be added soon is an information resource called NIHSeniorHealth, which the NLM is preparing in collaboration with the National Institute on Aging.

The 550 MEDLINEplus health topics have links to a database of ongoing and planned scientific studies—ClinicalTrials.gov. This database is a registry of some 5,700 trials for both federally and privately funded trials of experimental treatments for serious or life-threatening diseases. Most of the studies are in the U.S. and Canada, but about 70 countries are represented in all. ClinicalTrials.gov includes a statement of purpose for each study, together with the recruiting status, the criteria for patient participation in the trial, the location of the trial, and specific contact information.

There are several new NLM databases of interest to the public. One is "CAM on PubMed." This allows users to limit a MEDLINE search to articles about complementary and alternative medicine (CAM). The CAM on PubMed subset currently contains a quarter million references to journal articles related to CAM research. Another new online service is a Web site aimed at the special needs of the inhabitants of the far north. "ArcticHealth," as it is called, provides access to evaluated health information from hundreds of local, state, national, and international agencies, as well as from professional societies and universities. The new site has sections devoted to chronic diseases, behavioral issues, traditional medicine, environment/pollution, and environmental justice.

OUTREACH

The National Network of Libraries of Medicine (NN/LM) continues to be the NLM's primary collaborator in outreach to the biomedical community and to the public. The NN/LM consists of 8 Regional Medical Libraries, 150 resource libraries (at medical schools and other major institutions), and 4400 libraries at hospitals, clinics, and local health institutions. In 2001 the NLM competitively awarded new 5-year contracts to eight institutions to serve as Regional Medical Libraries. The goal of the Network is to

provide access to accurate and up-to-date health information for health professionals, patients, families, and the general public, irrespective of their geographic location. The NN/LM places a special emphasis on outreach to underserved populations in an effort to reduce health disparities. For example, there are programs to assist in remedying the disparity in health opportunities experienced by such segments of the American population as African Americans, Latinos, Native Americans, senior citizens, and rural populations.

One highly successful NLM outreach program has been strengthening Historically Black Colleges and Universities so that they can train people to use information resources in dealing with environmental and chemical hazards. Under this program, more than 80 minority institutions have received such training, and it was recently expanded to include a Hispanic serving college and a tribal college. NLM is using these schools as conduits to work with underserved communities in promoting high-quality Internet connectivity and the use of technology for research and education. The same NLM division that operates these programs also makes local awards to promote better information access for patients, families, and caretakers dealing with HIV/AIDS. In all these programs dealing with minority populations, NLM seeks to involve a wide variety of grass-roots organizations, from local health departments to churches, schools, and public libraries.

RESEARCH AND DEVELOPMENT

The Library remains at the cutting edge of research and development in medical informatics—the intersection of computer technology and the health sciences. It does this both through a program of grants and contracts to university-based researchers and through R & D conducted by the NLM's own scientists. The Library was a leader in the High Performance Computing and Communications initiative of the nineties and is presently working to ensure that the health sciences are prepared to take full advantage of the Next Generation Internet. NLM's Lister Hill National Center for Biomedical Communications conducts a wide range of research to improve biomedical communication and also oversees a broad-gauge telemedicine program and the Visible Human Project.

The Library has funded a variety of innovative telemedicine projects that demonstrate the application and use of the capabilities of the Next Generation Internet. "A Clinic in Every Home" is an especially promising telemedicine project with the Iowa Department of Public Health and the University of Iowa. Building on work successfully done under an existing contract with NLM, this project is providing a test-bed for medically underserved rural Iowa residents to provide them with access to high quality health care. The expectation is that using such a system will both raise the quality of health care and lower health care costs.

Applications involving the Visible Humans will also use the expanded capabilities of the Next Generation Internet. The Visible Human male and female data sets, consisting of MRI, CT, and photographic cryosection images, are huge, totaling some 50 gigabytes. The datasets are licensed to scientists at more than 1400 institutions around the world. Projects range from teaching anatomy to practicing endoscopic procedures to rehearsing surgery. One new aspect of the Visible Human evolution is the project to develop an extremely detailed atlas of the head and neck in collaboration with four NIH Institutes and the National Science Foundation. The application of cutting edge technologies in this project will allow interactive dissection of anatomic structure and "fly-through" anatomic relationships, for example, traveling down the optic nerve and viewing the ophthalmic artery and its tributaries.

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

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's third annual performance report which compared our FY 2001 results to the goals of our FY 2001 performance plan.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Jack Whitescarver, Acting Director
Office of AIDS Research

on
Fiscal Year 2003 President's Budget Request
for the National Institutes of Health

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 2003, a sum of $2,769,997,000 an increase of $255,043,000 above the comparable FY 2002 appropriation. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second performance report which compared our FY 2001 results to the goals in our FY 2001 performance plan.

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

THE EXPLODING PANDEMIC

The December 2001 AIDS Epidemic Update of the Joint United Nations Programme on HIV/AIDS (UNAIDS) states, "AIDS has become the most devastating disease humankind has ever faced." Since the epidemic began, nearly 60 million people worldwide have been infected with HIV. UNAIDS reported that AIDS has killed more than 22 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide. The impact of AIDS on developing nations and many

countries of the former Soviet Union is profound, with even greater potential disaster still to come. The UNAIDS report states, "the epidemic is driving a ruthless cycle of impoverishment." AIDS is reversing decades of progress from important public health efforts, lowering life expectancy, and significantly affecting education, agricultural output, and commerce of all kinds. Lost productivity and profitability, the cost of sickness and death benefits, and the decline in a skilled workforce in the developing world will have economic effects worldwide. AIDS is affecting the military capabilities of some countries as well as the international peacekeeping forces. In Africa, the epicenter of the pandemic, AIDS is sabotaging economic development, leading to massive social breakdown, and creating a generation of orphans. If the global spread of HIV/AIDS continues unchecked, South and Southeast Asia, and perhaps China will follow the disastrous course of sub-Saharan Africa. AIDS remains a serious threat in Latin America and the Caribbean. UNAIDS also reports that HIV incidence now is rising faster in Eastern Europe and Central Asia than anywhere in the world, with a 15-fold increase in reported new infections in the Russian Federation in just the past three years.

THE AIDS EPIDEMIC IN THE UNITED STATES

In the United States, the HIV/AIDS epidemic continues to expand and evolve, presenting new and complex scientific challenges. The Centers for Disease Control and Prevention (CDC) reported last month that the total number of individuals living with HIV in the United States is increasing as the use of antiretroviral therapies has prolonged the lives of HIV-infected individuals. At the same time, the rate of new HIV infections has not declined in over a decade, remaining at approximately 40,000 new cases each year. This means that the overall epidemic is continuing to expand. 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.

An additional concern is that although antiretroviral regimens have extended the length and quality of life for many HIV-infected individuals in the United States and Western Europe, unfortunately a growing proportion of patients receiving these therapies are now experiencing treatment failure. Some patients find it difficult or impossible to comply with arduous treatment regimens, develop toxicities and side-effects, or fail to obtain a satisfactory reduction in viral load even while adhering to treatment regimens. In addition, serious complications, including heart, liver, and kidney problems, insulin resistance, and body composition changes such as deforming fat deposits, have emerged in individuals who have been on long-term antiretroviral regimens. An increasing number of treatment failures are linked to the increasing emergence of drug-resistant HIV, presenting another serious public health concern.

COMPREHENSIVE AIDS RESEARCH PLAN AND BUDGET

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

The Plan establishes the NIH AIDS scientific agenda for the Scientific Areas of Emphasis of AIDS research: Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral and Social Science. As the epidemic expanded, we recognized that we also needed to take a planning approach that cross-cut these scientific areas. Thus, the Plan also addresses the critical cross-cutting areas of Racial and Ethnic Minorities; Women and Girls; Microbicides; Prevention; International Research; Training, Infrastructure, and Capacity Building; and Information Dissemination.

The Plan initiates the budget development process. Based on the objectives and priorities established in the Plan, the Institutes and Centers submit their AIDS research budget requests to OAR, focusing on new or expanded program initiatives for each scientific area. The OAR reviews the IC initiatives in relation to the Plan, to OAR priorities, and to other IC submissions to eliminate redundancy and/or to assure cross-institute collaboration. The law requires that the NIH Director and the OAR Director shall together determine the total amount allocated for AIDS research. Within that total, the OAR allocates the AIDS research budget levels to each IC based on the scientific priority of the proposed initiatives at each step of the budget development process up to the time of the Conference Committee. This involves consulting regularly with the IC Directors. This process allows the OAR to ensure that NIH AIDS research funds will be provided to the most compelling scientific opportunities, rather than distribution based solely on a formula.

The overarching themes that continue to frame the NIH AIDS research agenda are: prevention research, including development of vaccines, microbicides, and behavioral interventions, critically needed to reduce HIV transmission; 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.

TRANS-NIH COORDINATION

OAR plays a crucial role in identifying scientific areas that require focused attention and facilitating multi-institute activities addressing those needs. This is a two-way process. In some cases these issues are raised within OAR and shared with the Institutes; in other cases, an one or more Institutes may ask the OAR to bring other Institutes together to address an area of research or a specific grant or project. OAR can foster this research through a number of mechanisms, such as establishing working groups or committees; sponsoring workshops or conferences to highlight a particular research topic; sponsoring reviews or evaluations of research program areas to identify gaps or needs; and designating funds and supplements to jump-start or pilot program areas.

For example, a number of years ago OAR identified microbicides research as an area needing additional attention on the part of a number of Institutes. Microbicides research has proved particularly challenging, as there is no definitive clinical evidence as yet establishing that a product applied topically in humans can prevent HIV infection. Microbicides research requires a complex multidisciplinary and multisectoral approach by teams of scientists with a broad array of expertise, with increased pharmaceutical company involvement. To address this important need, OAR established a Trans-NIH Microbicides Working Group, comprised of program staff of relevant institutes and offices, which worked together to help plan the first international conference on microbicides and to spearhead the development of the NIH Strategic Plan for Microbicides. There are many more examples where OAR has played a key role in coordinating institute participation in a specific research project, such as the NIAID-sponsored multi-institute HIV Prevention Trials Network, and the Adolescent Trials Network, sponsored by NICHD and co-supported by a number of other institutes. OAR coordinated the efforts of NIDDK and other institutes in supporting a highly meritorious and innovative research project to comprehensively study the serious metabolic side-effects and complications of antiretroviral therapy. Insight gained from this multi-site collaborative study will have direct impact on the development of better tretment regimens for HIV-infected individuals.

INTERNATIONAL RESEARCH

To address the increasing urgency of the AIDS pandemic, the OAR has established a new initiative and strategic plan for global research on HIV/AIDS aimed at slowing the disaster and reversing its destruction of communities, economies, and nations worldwide. The Global AIDS Research Initiative and Strategic Plan reaffirms NIH's long-standing commitment to international AIDS research and will significantly increase research efforts in the coming year 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.

RACIAL AND ETHNIC MINORITIES

OAR has placed high priority on research to address the disproportionate impact of the HIV/AIDS epidemic on racial and ethnic minority communities in the United States. OAR is directing increased resources toward new interventions that will have the greatest impact on these groups and making significant investments to improve research infrastructure and training opportunities for minorities. OAR has provided additional funds to projects aimed at: increasing the number of minority investigators conducting behavioral and clinical research; targeting the links between substance abuse, sexual behaviors and HIV infection; increasing outreach education programs targeting minority physicians and at-risk populations; and expanding our portfolio of population-based research. OAR also has initiated a series of Training and Career Development Workshops specifically designed for racial and ethnic minority investigators.

SUMMARY

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

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Mr. Stephen A. Ficca
Associate Director for Research Services, National Institutes of Health

on

Fiscal Year 2003 President's Budget Request
for the National Institutes of Health 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 FY 2003, a sum of $632,800,000, which reflects an increase of $306,700,000 over the comparable Fiscal Year 2002 appropriation.

ROLE IN THE RESEARCH MISSION

The FY 2003 Budget establishes a new HHS Facilities Construction and Management fund that will finance all construction projects for NIH and CDC within the Office of the Secretary. The fund will allow HHS to prioritize and manage construction projects effectively.

The Buildings and Facilities (B&F) program supports the physical infrastructure required to carry out the in-house component of the biomedical research mission of the National Institutes of Health (NIH). In turn, the FY 2003 Buildings and Facilities budget request supports long-standing commitments to create, expand, and sustain a robust, modern, safe and secure physical infrastructure for the conduct of basic and clinical research across the spectrum of biologic systems and diseases. It also provides new, specialized containment facilities in which the United States will conduct research on a variety of biologic materials that present a health threat as emerging infections and/or bioterrorism agents.

The NIH B&F plan is the product of a deliberate strategic planning and priority setting process. This process is overseen by the NIH Facilities Planning Advisory Committee (FPAC) and captured in the NIH Strategic Facilities Plan. The FPAC, comprised of Institute Directors and other senior IC scientific and management staff, advises the NIH Leadership and Director on the long-range capital facilities investments that are needed to sustain NIH research programs and priorities. The FPAC is also instrumental in adjusting priorities as necessary to deal with unanticipated public health challenges and changes in national priorities. The goal of the planning process is to optimally meet the changing facility needs of the NIH research programs in the

Washington, D.C., region and across the NIH field stations with a mix of owned and leased facilities.

The NIH Strategic Facilities Plan is structured as a logical sequence of programs and projects orchestrated to enable the NIH to build facilities critical to new and expanding research initiatives and programs and to concurrently manage and maintain existing NIH real estate assets.

The construction program supported by the proposed FY 2003 budget request strikes a balance among three critical facility priorities: the creation of new facilities for new and expanding scientific opportunities, as well as for research on biologic materials that present a health threat as emerging infections and/or bioterrorism agents; the upgrading of existing facilities to keep pace with the changing requirements of ongoing NIH programs, and the responsible stewardship of the entire NIH real estate portfolio. The FY 2003 B&F proposal is organized into six broad Program Activities: New Construction; Essential Safety and Regulatory Compliance; Physical Security Improvements; Repairs and Improvements; Renovations; and Equipment and Systems. The FY 2003 request provides funds for specific projects in each of the program areas. The projects and programs enumerated are the end result of the aforementioned NIH Strategic Facilities Planning process and are the NIH's capital facility priorities for FY 2003.

The FY 2003 B&F budget request of $632,800,000 is an increase of $306,700,000 from the comparable FY 2002 level. As a result of this increase, the NIH will be able to fulfill its commitment to integrating neuroscience research in the John Edward Porter Neuroscience Research Center; maintain responsible funding support for the ongoing essential safety, renovation, repair and related projects that are vital to proper stewardship of the entire portfolio of real property assets; continue with the integration of the new Mark O. Hatfield Clinical Research Center (CRC) into old Building 10; increase the physical security of NIH facilities; and construct critically-needed, high-containment facilities on the Bethesda Campus and at Ft. Detrick.

The John Edward Porter Neuroscience Research Center will enable the integration of the neuroscience research community at the NIH. The Center is conceived as a place where the best and brightest scientists from many disciplines will collaborate in state-of-the-art laboratories to develop and evaluate therapies for some of the most complex problems in biomedical research. The Center will house researchers from nine Institutes and multiple disciplines under one roof. It will be designed to support high-priority research initiatives using innovative strategies in cell biology, neuroimaging and bio-informatics to better describe the link between biochemistry and behavior, to elucidate the nerve cell degenerative processes, and to explore other lines of inquiry that are emerging from the genetic mapping of the brain. New facilities are needed to support this vision because nearly all of the space that houses NIH neuroscience research is substandard. Current facilities for cellular and molecular neuroscience on campus are inadequate to meet the challenges of high-quality, high-risk research projects. The FY

2003 request would support the construction of the second phase of this facilities project; Congress appropriated funds for the first phase in FY 2001 and 2002.

The FY 2003 Building and Facilities budget request also contains major facility investments that are a response to the United States' heightened attention to Homeland Security. These include construction of a set of high-containment facilities at the Bethesda, Maryland, campus and at Ft. Detrick, Maryland, as well as a series of projects that will substantially increase the physical security of NIH facilities.

While NIH continues to take advantage of unique research opportunities for new treatments and cures, the recent tragic events have revealed the need for an expanded program of medical research on all aspects of bioterrorism. The capability to detect and counter terrorism depends to a substantial degree on the relevant medical science and basic research. There is an increased need for basic research to accelerate knowledge of the physiology and genetics of potential bioterrorism agents, immune system function, and response to each agent, and the pathogenesis of each disease, and for tests to rapidly diagnose, vaccines and immunotherapies to prevent, and drugs and biologics to treat diseases caused by agents of bioterrorism. The massive research agenda required to protect the American population against present and future attacks by these agents must include construction of facilities in which such agents may be safely studied. Facilities and procedures for the handling of these lethal agents with no threat to laboratory and clinical personnel or to adjacent communities comprise an integral element of the research program. These proposals for new construction, renovations and improvements are key elements to responding to the new research agenda while ensuring the continued vitality of the NIH biomedical research enterprise.

FY 2003 BUDGET SUMMARY

The FY 2003 budget request for Buildings and Facilities is $632.8 million. The B&F request totals $464.1 million for new construction composed of $4 million for the information technology infrastructure to complete the first phase of construction of the John E. Porter Neuroscience Research Center; $168 million to fund the construction of the second phase of the Center; $186.1 million to construct the Center for Bioterrorism and Emerging Infections-- new laboratory space on the NIH Bethesda campus for rapid response programs dealing with select infectious agents that may be used as weapons of bioterrorism and other emerging infections; $105 million to construct a Biosafety Level 4 (BSL-4) Lab/Clinic at Ft. Detrick, Maryland, that will provide the specialized, high-containment lab facilities needed to conduct biomedical research on the most dangerous and highly infectious diseases that could become or have been bioterrorism weapons; and $1 million to continue the Concept Development Studies program. There is a total of $6 million for essential safety and regulatory compliance programs composed of a combined sum 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. For physical security improvements, the request includes $80 million to bolster NIH's ability to provide a safe and secure environment for the conduct of the NIH mission on its sites. In addition, the FY 2003 request includes $56.5 million for the continuing program of repairs, improvements, and maintenance that is the core of the B&F program; $24.2 million for the Building 10 transition program; and $2 million to upgrade mechanical systems at NIEHS.

GOVERNMENT PERFORMANCE AND RESULTS ACT (GPRA)

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compared our FY 2001 results to the goals in our FY 2001 performance plan.

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

Mr. REGULA. I will withhold my questions, because I know members have other commitments.

Mr. Obey—he's on the Floor. Then we will go to Mr. Wicker.

Mr. WICKER. Thank you, Mr. Chairman.

Dr. Kirschstein, let me echo the laudatory remarks of my colleagues and just observe that in listening to them here and hearing my Chairman talk about the two great commandments, it occurs to me that you are somewhat like Moses——

[Laughter.]

GREATEST SUCCESS STORY

Mr. WICKER [continuing]. Looking out over the promised land and speaking to the children of Israel about what to expect in the future.

Let me just ask you, what is your greatest success story? You mentioned these amazing results in the first page of your testimony. Mr. Obey mentioned the fact that even back in our constituencies, the words National Institutes of Health are not very familiar, and people really still do not understand the NIH. If I go back to some civic club in my constituency and want to talk about the greatest achievement of the last two years of your directorship, what would be the first thing I should mention?

Dr. KIRSCHSTEIN. There are so many that it is hard to really single any one out. But I think it is the fruition of so many activities related recently to the basic science that has been performed by all the institutes, both as Mr. Obey said in general, and in basic activities of all related to diseases, the fruition of the fact that those findings and the clinical applications for them are somehow coming together and enabling us to really see a number of things that will be able to very directly benefit the health and well-being of the American public, both in prevention, in diagnosis, in treatment and in many cases in cure.

And the fact that while we used to talk in periods of 20 years before a discovery came to fruition in terms of something that could be applicable to the patient that time has begun to narrow. So now you will hear from my colleagues, and maybe each one of them at some point during their four days here will be able to tell you what they think of this. Because they may have a different view than I do.

But we will be able to tell you what has allowed this enormous opportunity to keep on providing more for the well-being of the public.

Mr. WICKER. Let me just observe to my colleagues on the Subcommittee, I have 24 mostly rural counties in North Mississippi. I write a weekly column that appears in most of the weekly papers. I think maybe for all of us on the Committee, it might be a good opportunity to take the fifth year of our doubling project and the occasion of your announced retirement as an opportunity to write a column for——

[Laughter.]

Mr. MILLER. She hasn't announced it yet.

Dr. KIRSCHSTEIN. I'll answer that in a moment. [Laughter.]

Mr. WICKER. Well, you're moving to another area of service for the NIH. As an opportunity to inform our constituents of some of

the really, really excellent accomplishments that we have made on behalf of science and health.

Dr. KIRSCHSTEIN. We would be pleased to. I think each of my colleagues attempts, and we have wonderful staff who help us, to translate what we have accomplished into what the public can understand. We have done that through many means, and we look for opportunities to talk to people, to have visitors come, Mr. Regula has had a number of visitors come and visit us. We hoped to have some people from the Chamber of Commerce, it didn't quite work out.

But we would be delighted to do all of that.

MUSCULAR DYSTROPHY

Mr. WICKER. Thank you also for your help with regard to the legislation which I sponsored, H.R. 717, concerning muscular dystrophy, particularly children and Duchenne muscular dystrophy. As you know, that bill has been enacted, signed into law by the President. I just wondered if you could let the Subcommittee know if you have been able to formulate, since it was signed December 18th of last year, if you have been able to formulate any plans as to how you might implement those centers of excellence and the things called for in that legislation.

Dr. KIRSCHSTEIN. Indeed we have. And we had arranged this session to be one in which I made this opening statement, and when questions were asked that were specific to diseases that are being studied in the Institutes, that we have a chair at the table and the Chairman very kindly agreed to have the institute director of that in charge of activity come forward. So if Dr. Penn would come up and answer that question, working in concert, the Neurological Disorders and Stroke Institute and the Arthritis and Musculoskeletal Diseases Institute, Dr. Katz, have begun to implement that.

Dr. PENN. Good morning. We indeed have had a major meeting in January of this year to begin to formulate and work on the new Act and the provisions of the new Act. So this involves Dr. Katz and the Arthritis Institute as well as the Child Health Institute. We met with representatives from the Parent Project for Muscular Dystrophy, with the Fascio-Scapulohumeral group, who actually were on the phone, and with the Muscular Dystrophy Association, MDA, who were at the table. We've agreed that we will definitely all work together, that we will formulate new research plans, that we will try to develop centers or something that will fulfill the mandate of centers, so that we get resources that everybody shares, we have registries of our patients, and we can move forward toward pulling back normal functioning genes.

I have to say that all of the groups at the table are together on this. We have since gone out to the Muscular Dystrophy Association meeting, their latest meeting on stem cells. One of our people was there. Muscle is a little different, so it may not be the usual stem cells that we worry about. But they are very interested in that. We are still waiting to facilitate gene therapy.

So we are very encouraged, and we are going to commit appropriate resources to this.

Dr. KIRSCHSTEIN. Let me add to that, Mr. Wicker, in fiscal year 2002 we estimate that we will be spending $23 million and we estimate $25 million for the muscular dystrophies for fiscal year 2003.

Mr. WICKER. Thank you, Mr. Chairman. If I could just conclude, I want to thank you for your staff coming into my office and discussing this issue in laymen's terms that even a Congressman can understand, and helping us amend the bill in such a way that you all felt that it could be more workable. It's a great result, and I thank all my colleagues who helped me with that legislation, particularly you and your staff.

Dr. KIRSCHSTEIN. We thank you, Mr. Wicker.

Mr. REGULA. Mr. Obey, you're up.

SCIENTIFIC OPPORTUNITIES

Mr. OBEY. Thank you, Mr. Chairman.

Doctor, I would just like to ask about three or four basically boilerplate questions, because I think some of them need repeating again and again. The most difficult job this Subcommittee faces in dealing with your budget, outside of assuring enough resources for it, is to deal with every well-meaning group in the land that wants to come in and have Congress specify a specific amount of funding for a specific disease. When you have people in your office who are suffering from Parkinson's or suffering from cancer or Lou Gehrig's disease or you name it, it's very difficult to explain. Because they do not want to hear generalities. They want to know what you are going to do about their problem. I understand that.

Nonetheless, if you were sitting with those folks, what would you say to them to make them understand that they do no one any long term favors if they insist that we start earmarking funds for specific diseases at specific levels? How would you explain to them that scientifically that's the wrong thing to do if you really want to solve the problems they are concerned about?

Dr. KIRSCHSTEIN. They come to my office, too, Mr. Obey. And it is the most difficult problem. It is heart wrenching to see these patients, there is no question about that. We listen to them carefully. And we consider the status of where we are in regard to that particular disease or the broader field of science that is encompassed by studies in that disease. We also know that as we have progressed in our knowledge, it is not any longer really as possible to compartmentalize that research done on Parkinson's disease is solely for Parkinson's disease or research done on neurobiology, neurosciences will not be important in many other areas.

We seek opportunities by calling together, the scientific experts as well as the people who represent either themselves, because they are ill, or family members who are ill. We did that most recently on two separate occasions, as recently as December if I am not mistaken, or early this year, I cannot remember exactly, the Parkinson's people. We sat together and talked about what were the scientific opportunities that could be directly related to that disease, what are the therapeutic possibilities, what do we not know, what can we learn if we study something very basic. And we put together a plan of how we can accomplish it. We try to be very honest with the people and say, if we do not think that the scientific opportunities are ripe to make something happen, we feel

that we must move further, we would not be promising you something we cannot accomplish.

DOUBLING THE NIH BUDGET

Mr. OBEY. On your budget, again, both parties pose for holy pictures about the doubling of NIH over five years, or roughly doubling. But one of my concerns is what happens when the five year window is over. If you take a look at the out-year situation, my understanding is that the President's budget envisions an increase for fiscal year 2004 of just $576 million, or 2.1 percent, in contrast with the huge increase we have this year. And for 2005 and 2006, the projected increases are the same.

What would be the impact on NIH if you only got a $576 million or 2 percent increase in fiscal year 2004?

Dr. KIRSCHSTEIN. Mr. Obey, we have thought about that, and we are very aware also that the President's budget has a 2.1 percent increase. We will study the situation very carefully, and by appropriately looking at where those funds should be used and constraining some areas and thinking carefully how about to go about it, we believe that it will be possible to maintain in that budget, a reasonable number, not very different, in fact approximately the same as the number of new and competing research grants as we have been doing this year.

Mr. OBEY. Let me ask about that. Is it not true that the cost of just providing year to year renewals of ongoing research grants totaled about $1.2 billion last year and about $800 million this year?

Dr. KIRSCHSTEIN. Yes, sir.

Mr. OBEY. In both cases, considerably more than the entire NIH-wide increase the Administration is proposing for 2004?

Dr. KIRSCHSTEIN. Yes. But there will be some cycling. Some of those costs were due to very large grants. And we may have to look at ways to do something about this. We will try our very best to maintain whatever momentum there is.

One thing I think we have to say is that it is very clear that one way or another, biomedical research will progress. It may take longer, but it will progress.

Mr. OBEY. But you cannot, can you, assure us that a $576 million increase next year would allow you to fund renewals or that you would not have to be cutting grants for existing projects?

Dr. KIRSCHSTEIN. I cannot assure it, but I will try.

Mr. OBEY. I am sure you will try. But I think the important part of that sentence is that you cannot assure it. I mean, I frankly do not think the Administration set out to produce this result. I think those small increases are all that they can afford if they are trying to fit into the budget area the ever-increasing costs of their tax cuts. I do not expect you to comment on it, but I feel free to. Because I think what we are seeing is that as the costs of those tax cuts ramp up a lot of things that we know shouldn't happen have to be included in the budget in order to make room for it.

Mr. Chairman, I have another question for the record, but I'll submit it. My time is up. I have another question concerning the National Institute for Environmental Health Sciences.

Mr. REGULA. Mr. Hoyer.

SUCCESS RATES

Mr. HOYER. Thank you very much, Mr. Chairman. I share, as you will not be surprised, Mr. Obey's concerns.

I remember back to a colleague of ours who I mention often, because I was so impressed with the tenacious focus he had for NIH, and that's Joe Early. You remember Congressman Early from Massachusetts, who made extraordinary contributions to this effort, and very frankly, Congressman Early, in the doubling of the budget of NIH with the rhetorical support of Mr. Natcher, would have said, that's fine, but it's not enough. Because the opportunities to effectively apply more resources to overcome illness and disease and have such a big economic payoff in terms of the invested money.

I've mentioned Dr. Lowe, the dental, his report. Tony, you ought to have this report as well. In terms of the investment in dental research, Susan, you'll probably remember this, investment in dental research, over all of the time that we had been appropriating money for NIH, and this was maybe ten years ago that he made this analogy, over all the time that we had been funding NIH, were paid off four or five times over in one year's savings, in the dental field.

And obviously, it would be multiplied many times over, for instance, in terms of AIDS, in terms of the lives that we have extended, the quality of life that we have extended, the workers that we have kept on the job, the families we have kept. That applies to all the institutes, as was mentioned. It was Dr. Fauci's focus, but it is the focus of all of us as well.

In any event, we are going to have to be pretty tenacious in making sure that we do not back up. Let me ask you, in that context, what is our pay line projected to be in 2003?

Dr. KIRSCHSTEIN. About 30 percent success rate.

Mr. HOYER. That's an average, I take it. Do you know what our lowest pay line will be in the institutes? Because we've been down in the middle teens, as you know, from time to time.

Dr. KIRSCHSTEIN. Several of the institutes are very low. But they are institutes that have been traditionally not paying as many individual research grants but have been building their portfolios with large groups, particularly the National Center for Complementary and Alternative Medicine. So I do think that that counts. There are a couple that are in the 14 and 15. But the vast majority are 30, 29, some of them are higher than that. We think that is a very good pay line.

Now, the other thing about that and about what you've been saying is, many of us have been consciously concerned about, and I believe I spent some time talking about this at last year's hearing, about making sure that we do not have a sudden drop. So we've been talking about one time investments in large instrumentation, in data bases, in repositories of cells and chemicals. So some of this will be flattened out as a result.

Mr. HOYER. Mr. Chairman, you weren't on the Subcommittee when Joe Early was here. You were here with him on the committee. But one of the things that Congressman Early was concerned about, and Dr. Kirschstein is now speaking about, the fluc-

tuation of pay lines not only adversely impacts current research, but what it really does, it discourages very talented people from going into basic biomedical research because of the inconsistency of resources available for basic research.

So that's what David Obey was speaking about. I think we all need to be concerned about keeping that pay line up over the 25 or 30 and particularly now, because the opportunities are even greater than they were 10 years ago. I would imagine now the level of so-called good research that peer review has shown is a significantly higher level than it was even 10, 15 years ago.

Dr. KIRSCHSTEIN. Absolutely.

LOAN REPAYMENT PROGRAM

Mr. HOYER. Let me ask you two quick questions. I was going to ask about security and what money was spent on it. I'll do that for the record. I was a sponsor of the Clinical Research legislation and I have some comments about it. But let me just ask the question. When will the NIH move forward and initiate the graduate training in clinical investigation awards? That was something that we had anticipated. What's the status?

Dr. KIRSCHSTEIN. The National Center for Research Resources is implementing that program now through the program that it has to enhance clinical research activities, so that there will be ability to train and get stipends and tuition. And loan forgiveness, which is probably the most important thing that came out in some ways for the general issues related to the clinical research enhancement. Dr. Vaitukaitis can expand on that if you would like to.

Mr. HOYER. My time is very limited, and I would like to get that. But one of the concerns I know that the advocates and those who expected this to have a broader impact are concerned about the budget of one institute being able to accomplish the objectives on that. Are we going to apply it more broadly?

Dr. KIRSCHSTEIN. The institutes are starting off by applying the loan repayment program very broadly. At the moment, the National Center for Research Resources has taken up the graduate education activities. This is post-M.D., graduate education post-M.D. I think as this progresses we will evaluate it and see whether we want to go more broadly.

Mr. HOYER. I know my time has expired. I have another question on that which I will submit. And I apologize, but my time has expired. Not only that, like Mr. Obey, I have a commitment at a quarter of twelve. This is the time when I think all of us ought to probably just have one subcommittee. [Laughter.]

But that's not the case.

Dr. KIRSCHSTEIN. Thank you, Mr. Hoyer.

Mr. HOYER. Thank you, Doctor.

Mr. REGULA. Mr. Miller.

APPOINTMENT OF DIRECTORS

Mr. MILLER. Good morning. John Porter used to talk about this as being the crown jewel of the Government. Unfortunately, not too many people know about some of the things that take place within this great Institute. Mr. Hoyer actually and Mr. Wicker both talked about what's been done in dental. Mr. Wicker asked what are you

proud about. The problem is, so much is hard to focus in the credit. Yet when we're talking about this kind of dollars we just need to try to do a better job of really communicating the great successes we have here.

One area I always think is that we should encourage every medical institution that gets grants to invite their local member of Congress to come in. I do not have one in my district, but I have one not far away, and I have visited the University of South Florida, the Moffett Cancer and the medical school and such. It's so impressive, not just to visit out at your facilities in Maryland.

So anything we can do to encourage that, because that just helps people educate that this $27 billion is not all spent out in Bethesda, Maryland.

Let me ask a clarification question. Dr. Zaroni has been nominated, he has to be approved by the Senate, is that right?

Dr. KIRSCHSTEIN. The position of Director of NIH is a Presidential appointment, subject to Senate confirmation.

Mr. MILLER. Sometimes that can take months and months and months. Do you have any idea of a time?

Dr. KIRSCHSTEIN. No, sir.

Mr. MILLER. Is that the only one? The other acting directors can be appointed, I see the new Director of the Cancer Institute was appointed directly by the President. But he's the only one appointed directly?

Dr. KIRSCHSTEIN. The Director of NIH is the only one that requires Senate confirmation.

Mr. MILLER. Can any of the other acting directorships be addressed before Doctor—I do not want to——

Dr. KIRSCHSTEIN. Mr. Miller, I have in place search committees to be looking for the directors of all the institutes which have acting directors at the moment. Those search committees are moving ahead very rapidly. We have almost finished the search for two out of the group. Names will be submitted as soon as possible to the Secretary who makes the appointments.

I think probably the Secretary will want to discuss with others how he should move forward in regard to the fact that I am doing that as an acting director. In the time I have been Acting Director, however, we have had three or four important positions open. Two of them are directorships of institutes. I recommended to the then-Secretary two of our institute directors who have been on board for at least a year and one of them for almost two.

CLINICAL ACTIVITIES

Mr. MILLER. The focus of NIH has been basic research. Now we are talking about more clinical research. Mr. Hoyer brought it up, and you are talking about translational research. I know it's hard to define, I know it's a not a definite line between clinical and basic research, but whether it is the human genome project, basic, is there a focus as far as a change or a shift in emphasis?

Dr. KIRSCHSTEIN. Yes, I think so. First of all, I would say that the focus of NIH is on health research, biomedical research. It is not to do research in the basic sciences in a vacuum. It is to do research that will in one way or another be applicable to either pre-

venting, diagnosing, curing, treating or ameliorating the ills, the diseases, from which the public suffers.

Now, very often, in order to do that work, it requires the use of the most fundamental model systems, organisms like bacteria and viruses, animal models all the way through to clinical studies. But it is a continuum which would not be possible if our goal was not continuously to realize the health mission. That's why we're called the National Institutes of Health. We are not called the National Institutes of Biomedical Research. I think that is a real differentiation.

Mr. MILLER. As far as resources, shifting a little bit more towards percentage-wise, as far as clinical rather than basic?

Dr. KIRSCHSTEIN. We are beginning to move definitely more toward this.

Mr. MILLER. Can you really define which is clinical or basic?

Dr. KIRSCHSTEIN. We put figures together every year on what we spend on basic research and what we spend on what's called more applied research. And the numbers are changing. They've gone from 60 percent basic down to 57 percent in 2003, and up from 39 and a half percent to 43 percent on applied, which is clinical. So the emphasis that I have presented in the last two years, two of the three times that I have been testifying, and as I said today, has been on clinical activities.

STEM CELL REGISTRY

Mr. MILLER. Can I ask one more question? This could be a long question, but we will keep it real short, on stem cell. Would you give us an update of the situation on stem cell research and how many lines are available, how many grants have been made? Is it slower or faster than expected? What is the expectation?

I do not want to make this a long answer.

Dr. KIRSCHSTEIN. Dr. Baldwin has been following the details. I could probably try, but she will give you a quicker answer.

Dr. BALDWIN. There are 78 lines available now. We have added some lines since the stem cell registry was first posted. That was a very important step, because anyone who wanted to do research in human embryonic stem cells has to be able to pick a line off that registry. We are very pleased to have added lines to that registry.

Mr. MILLER. How many are there now?

Dr. BALDWIN. Seventy-eight.

Mr. MILLER. How many were you expecting when you announced?

Dr. BALDWIN. About 64. We have also extended the receipt date for the fall applications. If someone were really ready to do research right away, we made accommodations to be able to receive these applications. And we in fact got a number of applications in. We got the nine on that receipt date. We have had more come in for February 1st receipt date. They are in review now.

We are also accepting administrative supplements. We have received about a half dozen of them. And you might ask why haven't we actually made awards. This is a new area of research. Applicants and scientists want to take time to prepare their applications, and they may want to develop some preliminary data. They

want to make sure that when they come in with an application, they have a really sound one.

So I have not been surprised by the pace of this. It would be very unusual if the scientific community just stopped what they were doing and suddenly picked up an area that they had not been able to work in with Federal funding before and flooded us with applications. We see the rate of submissions increasing over time. We are working at all the pieces that have to be in place. We have infrastructure awards ready to go to make sure that the people who have the stem cells are able to supply the investigators who want them.

Dr. KIRSCHSTEIN. Many of the institutes have put out, after the President's announcement, requests for applications. So we are moving apace.

Mr. MILLER. Do you feel you are behind schedule or about on schedule? I guess it's hard because it is so new.

Dr. KIRSCHSTEIN. It is hard to say.

Dr. BALDWIN. Those of us who have been doing this for a long time have a sense of the pace at which the community will respond. I would say we are about on target.

Mr. MILLER. Thank you. Thank you, Mr. Chairman.

Mr. REGULA. Mr. Cunningham.

ACKNOWLEDGEMENT OF DR. KIRSCHSTEIN

Mr. CUNNINGHAM. Thank you, Mr. Chairman.

I want to also thank you, Dr. Kirschstein, and when they asked you about your accomplishments, you were a little remiss in talking about your own accomplishments. Let me note just a few that I saw.

I was concerned when John Porter left as Chairman, I was concerned on who would take over Chairman of this Committee, I didn't recognize someone that I thought could do as good a job. I am happy to say, I think Chairman Regula has done a good job. I do not like one vote he cast on the House Floor, but in this Committee, he did pretty good. [Laughter.]

Mr. REGULA. I like all of yours. [Laughter.]

Mr. CUNNINGHAM. But I want to thank you first for the availability of your department. I found that sometimes you comment to a doctor that hey, can you come and see me, I want to talk about this. They literally tree you until you do meet with them. The availability has been, and the responsiveness, unlike any other Department, I think, and that includes the Department of Defense. You have been responsive.

When I was over there in a visit, watching the film on Phyllis and meeting Phyllis, what an opportunity, that young lady with Parkinson's and the advancements. She had been given back her children and her grandchildren, they had a grandmother and a mom. The oncology, my daughter interned over there in the oncology lab and also the cardiology lab. By the way, she has a sub-med in, she's gone liberal on me, she wants a women's health studies over there this year. [Laughter.]

But she's got an application in, and I support it. [Laughter.]

OCULAR ALBINISM

Who happens to be the gentlelady who has agreed to give a talk to my daughter's group at Yale, I offered to talk and she wouldn't let me. She let the gentlelady. And I want to thank you for that as well.

But also, the outreach. Dr. Varmus was the head of cancer research, and now Dr. von Eschenbach. The only bad thing about him is he's not Irish. But we've already met. When you talk about another accomplishment, the outreach of the Department, the highest rate of prostate cancer is in African-Americans. You know, D.C. has never had a town hall meeting in that. And Doc has volunteered to do that, as well as UCSD. Those kinds of things out in our communities to let people know what you are doing I think is monumental in health.

I have a dream that you can help me with, and we have talked about it, not only making permanent the Office of Women's Health, but also an office of Men's Health, not to be competitive, but to work in collaboration and coordination, to get the information out of all the things we find, of what the advances are. There is a report due that you can help me with on ocular albinism. My adopted son, my son was adopted, and when I adopted him they told me he may have dyslexia. Fortunately, it didn't happen, didn't come to fruition. But ocular albinism is a hereditary disease that affects vision in children that can be distorted. If you could give me a report on that, our language asks that, I would appreciate it.

Dr. KIRSCHSTEIN. I am sure that Dr. Sieving, the Director of the Eye Institute, would be pleased to do that. Dr. Sieving.

Dr. SIEVING. I am pleased to be here. I am one of the new institute directors who came on board this last year through the efforts of Dr. Kirschstein. I am pleased to be here.

The request to address some activity on ocular albinism is very important. Ocular albinism is a developmental issue for vision. It affects a number of young people, and it gives us the opportunity to look both at the genetics of the disease, how one might ameliorate this ultimately, and the interactions of the genes with the development of the eye. We have a mechanism to solicit grants and expect to be funding about $3 million worth during fiscal year 2002.

EARMARKING DISEASES

Mr. CUNNINGHAM. Thank you. One last question. I have been against earmarks. I do not believe members of Congress should say that the Department should go in this direction or that direction. You all are the professionals. I notice, and listen, I am a cancer survivor and I want research in cancer. But I notice the President has earmarked money for cancer, prostate cancer. I do not think it's enough.

But at the same time, I always want to give the Department the flexibility to act, whether it's with Dr. Sieving or with Parkinson's or Alzheimer's or those diseases. Can you give me a brief explanation of how you see this earmark? Is it positive, negative?

Dr. KIRSCHSTEIN. The discussion of what should be the right number for any disease entity is one that we could have very

broadly. The President has a deep commitment not only to biomedical research, which he made evident by presenting, for the past two years, the yearly increment for the doubling, but also a deep and abiding commitment to cancer research. He and we are aware that very broadly, the National Institutes of Health supports cancer research in one way or another.

About 85 percent of that is supported by the National Cancer Institute. But the remaining is supported by the other institutes doing studies, not only of a basic nature, but perhaps on an organ system which is very susceptible to cancer, prostate being one of those. Therefore, we can all gain through this inter-institute effort, including interdisciplinary effort. There is much to be done by many, many institutes. I think we all gain and learn a great deal about other diseases by doing cancer research as well as cancer related research. That is the statement.

Mr. CUNNINGHAM. Thank you. I yield back, Mr. Chairman.

Mr. REGULA. Ms. DeLauro. We have only one vote on, I think. So if we could keep going.

RECOUPMENT OF FEDERAL RESEARCH FUNDS

Ms. DELAURO. I will do that. Thank you very, very much, Mr. Chairman. I will try to move quickly and I will enter some questions into the record.

Welcome. It is wonderful to see you all here this morning. I have a question that has to do with recoupment of Federal research funding. You know, I am a very, very strong proponent, as you all know, of NIH research and the whole issue of doubling the budget has been very important to me.

But I am also concerned about the amount of money, the public money, that gets invested, and in cooperation, if you will, with private companies, whether they be pharmaceutical companies or others in the broad range of companies in which we work together. When I first came 12 years ago, I testified on behalf of the opportunity to work together with Bristol Meyers Squibb with a CRADA on Taxol, etc. We moved forward in those developments.

But again, what I want to do is begin to ask some questions about, when these things move along, and they are in the public domain, how in fact do we recoup any of the profits, if you will, that then go back into the NIH to help to do the kinds of things that we need to continue to do and to extend that budget, if you will? It's in essence trying to get the most from federally-funded research.

Can you let me know, and if these questions are too long and you can get back to me on this, I am perfectly fine, given that we have to go to vote. I want to outline how basic research we fund at the NIH leads to the creation of new drugs, do we have a mechanism at NIH for recouping funding or some of the funding, and if so, how much of that funding do we recoup.

Would you, in light of the biotechnology revolution, will you support a more in-depth study which would analyze how NIH's research money results in a new drug? For example, the study might look at various organizations that are involve din the process, how they interact, who incurs the risk in drug development and how much and who makes the profit. I think this kind of an analysis

could serve as a kind of baseline for further study of how much the Federal Government recoups from its research and a road map, if you will, of how we can make improvements.

We are again always interested in trying to stretch that research dollar. We do this, and I am not sure of what we are getting back in order to help us increase and multiply, if you will. Maybe I should just do that and leave this for the record. It is a lengthy question.

Mr. REGULA. When we get the transcript with the question, we can get it for the record.

Ms. DELAURO. I can get it to you.

Dr. KIRSCHSTEIN. We have data, and we have mechanisms for doing that, both in place within the NIH intramural program and in some other areas. But it is a very long question and we will provide the data.

Ms. DELAURO. Please. What I would very, very much like to do is work with all of you on this issue. It is an issue which I am very, very concerned about, and one I think we need to really examine thoroughly. I think it would be helpful for the rest of the Committee as well. And I will submit my other questions for the record as well.

Thank you very, very much.

[The information follows:]

RECOUPMENT OF FEDERAL RESEARCH FUNDING

There is no standard pattern or process for the development of discoveries from basic research. New discoveries may arise out of a large research project but often are ancillary to the main objective of the research. The findings can come from working around obstacles or through serendipitous discovery.

Most basic research discoveries are early-stage including proofs of concept, mechanisms of action, and basic interactions. They can include new compounds or chemicals. However, these discoveries require further research and development to demonstrate proof of principle and bring them to practical applicability.

We should make it clear that the NIH is not in the drug development business. We do not develop new therapeutics and simply hand them over to companies to manufacture and distribute. The NIH needs partners, licensees, to invest significant resources to conduct the further development required. This is a high risk venture for those who wish to pursue the development of these technologies.

Typically, technologies need to be further developed with the combination of other technologies to eventually create a product that can have the anticipated effect without side effects that would deter their use. That process of development of new products is long and expensive. It can take years of development and many of these promising new discoveries fail to become efficacious and safe drugs.

MECHANISM FOR RECOUPING FUNDING

The NIH licenses technologies that originate from laboratories at the NIH. In exchange for licenses, the NIH receives royalty income which includes payments even before a technology comes to the marketplace. If and when an NIH technology becomes a part of a product that reaches the market, the NIH receives a portion of the sales as royalty income. By law, the income is used to provide inventors with a share of the royalties, pay for patent and other technology transfer related costs, with most of the funds being returned to the laboratory to support further research. Last year, the NIH generated more than $46 million in royalty income. Over the past 7 years, we have generated more than $260 million in royalty income. The last report from the Department of Commerce indicated that the NIH is responsible for two-thirds of the royalty income generated by the entire federal government.

Recipients of NIH funds operate in essentially the same manner as the internal NIH inventors. They license technologies for further research and development and receive royalty income that is used in a manner similar to that used by the NIH. The NIH does not receive a share of income generated by recipients from licensing of their government-funded discoveries.

RECOUP RESEARCH FUNDING

We believe that a recent report may address a number of the questions you have raised. The NIH submitted a report to the Congress in July 2001 in response to its request in Congressional Conference Report for a plan to ensure that taxpayers' interests are protected. That report concluded that the taxpayers have greatly benefitted from new diagnostic, therapeutic and vaccine products that were developed and have extended life and improved health. In addition, the study cites a report by the Congressional Joint Economic Committee issued in May 2000 entitled "The Benefits of Medical Research and the Role of the NIH." That report concluded that the taxpayer receives the economic benefit of a return of $15 for every $1 invested in the NIH. A copy of the report has been provided to the Committee and is available on the NIH website, http://www.nih.gov/news.

The report does not provide specific information on the amount of risk and profit of the various parties to the drug development process. That type of study would require the full cooperation of industry and access to business confidential information that is not available to the NIH.

Mr. REGULA. The Committee will be in recess. Mr. Sherwood will be back and he will preside for his questions. So if you will bear with us.

Dr. KIRSCHSTEIN. Certainly, sir.

[Recess.]

EPIDEMICS OF DIABETES AND OBESITY

Mr. SHERWOOD [assuming chair]. Well, after our short break, I am sure the Chairman will be back in a hurry. But we will just proceed a little bit, if that is all right with everyone.

Doctor, I wanted to ask you about diabetes. Everything we have heard from both CDC and from Secretary Thompson has identified diabetes as an epidemic, and that they have changed the name from adult onset because of obesity in young folks and the huge, huge increase that we are having. But can you help me with the fact that in light of this drastic increase, the percentage of NIH budget devoted to diabetes since 1987, if I am correct, has decreased? I wondered if you would comment on that or if you have some ideas for us.

Dr. KIRSCHSTEIN. Mr. Sherwood, we have made enormous progress and have been providing resources for diabetes research in what I consider to be a very significant manner. As you look at percentages, that may be true, but the growth of the field has exploded. Dr. Allen Spiegel, who is the Director of the National Institute of Diabetes and Digestive and Kidney Diseases, would be pleased to expand on that.

Dr. SPIEGEL. Thank you. You are indeed correct that all the CDC epidemiologic data, show that both obesity and type 2 diabetes are continuing epidemics. The public health problems have increased dramatically even between 1990 and 2000, which is the period of their most recent data. As you astutely pointed out, the fact is kids and adolescents, are now showing up with type 2 diabetes. This will be emphasized in a *New England Journal of Medicine* paper from Yale researchers that we are going to see published this week. So it is highly prevalent, both obesity and even now, impaired glucose tolerance, a pre-diabetic state.

However, as Dr. Kirschstein implied, we are attacking this problem vigorously. There is cause for hope and the possibility of reversing the epidemic. Specifically, for type 2 in kids, we together with other institutes such as the National Institute of Child Health

and Human Development, are funding centers around the country for research on both prevention, as well as treatment. We are testing school-based, community-based and family-based interventions to prevent this problem and to treat it in those already affected.

The greatest cause for hope, though, is the result of the NIDDK's major multi-center trial that the Secretary announced in a press conference August 8th of last year. This is a 3,200 individual multi-center trial called the Diabetes Prevention Program, which showed that in individuals at high risk for development of type 2 diabetes, this disease could be prevented. We achieved a 31 percent reduction in the development of type 2 diabetes using a drug, Metformin, and a 58 percent reduction using a lifestyle intervention involving modest changes in diet and exercise.

Our challenge now, as a Nation, is to translate the results of this landmark clinical trial, so we can reverse these grim statistics.

Dr. KIRSCHSTEIN. Let me add, Mr. Sherwood, that in the session we will have tomorrow called From Bench to Bedside, we will have a number of the institute directors talking in more detail about how they have gone from research to the bedside of the patient and beyond. Diabetes will be one of the subjects.

TRANSLATING DIABETES AND OBESITY RESEARCH FUNDING

Mr. SHERWOOD. What you have just told us leads into my next question, in which you talked about early in your testimony. What we have heard from SAMHSA and the National Academy of Sciences, Institute of Medicine, is that as you said earlier, there is a 15 to 20 year lag between the discovery of effective forms of treatment and the translation into routine patient care.

Isn't that exactly where we are with diabetes? Is it acceptable in this country that our delivery system, that it takes us so long to get the good work and the new knowledge that we have out into practice? I think diabetes maybe is a wonderful example of that. You have told us that obesity in children is such a problem of diabetes. Yet we do not seem, I do not see the links between behavior and our research. Where do you reach more young people than in public school?

We have always had some physical training classes, or physical exercise classes in school. They have become a little bit passe lately, sort of out of touch, people think. I think we have to get something out in the public that reduces this obesity among the kids. I am interested in your comment on that, as well as the general lag.

Dr. KIRSCHSTEIN. We totally agree with you. Probably altering behavior, research on altering behavior is something that needs a great deal of attention. It is so easy for children to sit in front of a television set as opposed to getting out and exercising. Dr. Spiegel probably wants to talk about some other studies in that regard.

Dr. SPIEGEL. The effort to combat this epidemic of obesity and diabetes is really a trans-NIH effort. In fact, it is a trans-Department effort. The Secretary himself is clearly passionate about it. I know this from hearing him speak about obesity and its association with type 2 diabetes on multiple occasions.

In 1999, many of the institutes supported innovative pilot projects for obesity prevention. These were targeted at all age

ranges. For example, women during pregnancy gain significant amounts of weight and then find that very difficult to lose. Pregnancy is a high-risk period. Dr. Kirschstein has already mentioned TV watching. In one study kids were not allowed to watch TV unless they pedaled a stationary bike. During that period of time, they lost weight and watched less TV. [Laughter.]

Mr. SHERWOOD. That's a win-win.

Dr. SPIEGEL. Absolutely. As a Nation, we have to realize that obesity is not a cosmetic problem. It is a health problem. A Rand study just indicated greater health care costs from obesity than from either smoking or drinking alcohol.

We have to mobilize against the environmental factors that predispose to obesity.

Mr. SHERWOOD. That might not be the way we want to sell that. [Laughter.]

Dr. SPIEGEL. Through positive approaches and messages, we can make the environment more conducive to exercise and less conducive to eating the wrong foods and to eating excessively. This requires not just an NIH effort, but a national effort.

Mr. SHERWOOD. Thank you very much. Mr. Miller.

Mr. MILLER. I think Mr. Jackson wants to go now.

Mr. JACKSON. I have a small emergency, I will be right back.

EARMARKS

Mr. MILLER. I have a chance to ask a couple more questions. Thank you, I am delighted.

First I want to follow up on a question Mr. Cunningham asked. That was about this issue of earmarking, and it is a slippery slope that I think you all are concerned about, as we are. You read in the paper about Mississippi wants to earmark some money and you hear the Senate wants to earmark some money. But actually, when the Administration's budget request has an earmark for cancer, I mean, my wife had breast cancer, my father died of lung cancer, I fully support it.

But it is an earmark, is it not? So I am not opposed to it, but if we are going to be opposing earmarks that Mr. Sherwood would have earmarked X number of dollars specifically for a diabetes program in his district in Pennsylvania, that's what we want to basically avoid to give you all to have a chance to have peer reviewed research. But it starts off when you all do an earmark of your own for us to avoid earmarking.

Dr. KIRSCHSTEIN. There is no question that a decision was made to specify a specific amount for cancer related research. I want to emphasize that, because research related to cancer also is of an enormous benefit to research, in other areas as well. And we do have an interdisciplinary field in which we feel that what is learned about one disease and one entity is important to the other.

Dr. Fauci can give you examples of why we were able to move forward so rapidly when AIDS emerged as a disease, because of what we had learned about some cancer viruses which are related to the AIDS virus in certain ways. So I think we have to be very aware of the breadth of the science.

Mr. MILLER. I understand. I am just saying, you make our job more difficult on this issue of earmarking. Some people have ana-

lyzed the way money for cancer, for example, and divide it by the population, the number of people impacted by cancer versus the number of people impacted by AIDS. They say, look at the huge disparity. That is not the way we should look at it, either.

So I understand. Let me switch to a slightly related issue. I have gotten a little more sympathetic to this issue about earmarking. My two colleagues on either side of me are not here, both good friends, but it concerns the geographic spread of the money. Both Mr. Istook from Oklahoma and Mr. Wicker from Mississippi make a case, their States have not gotten—not that they should have a fair share, I mean, I do not know where Florida rates, and that is not the critical thing, but we have some fine medical institutions that compete. I am sure Boston gets a very nice share because of all their institutions, or New York City.

And there is a program to help bring States up. Again, we should not earmark just for Pennsylvania, which has a great school, but Mississippi, or those on the lower end of the scale. How are we addressing that issue without getting—there is some earmarking, I guess, in a separate program. But how are we addressing that? They should be asking the question, not me.

Dr. KIRSCHSTEIN. Mr. Miller, 23 States and the Commonwealth of Puerto Rico probably share less in the funding that is received from NIH than do the remaining States. We have been concerned about that for a number of years, because there are possibilities and there are biomedical research institutions within those States which are doing fine research.

So in order to provide the opportunity for the biomedical researchers in those States, or individuals who would like to join their faculties, because there is something about a critical mass of scientists that leads to the ability to have a broad portfolio, we have provided a sum of money to each of the States to begin to develop programs. We are developing activities. We will continue to do that. That money will be increased in the President's 2003 budget.

We will work——

Mr. MILLER. How much money is that? How big a program is that?

Dr. KIRSCHSTEIN. It is going to be $185 million in fiscal year 2003.

This is not earmarked for an entity, it is not earmarked for a disease. It is to allow a State which, because of one fact or another, has been unable to develop the program it needs. It starts with asking that the State educational institutions, develop either one or two consortium efforts in which any school of higher education, junior college, college, professional school in the biomedical sciences, allied sciences, graduate schools, universities, work together to find some facet of activity in that State or develop some facet of activity in that State which can be brought to fruition. We will give them support for a defined amount of money to be divided equally among those 24 entities for three years, possibly renewal for three more.

Mr. MILLER. Just getting the broad support, because that's the very original question I asked, that we need for NIH, and understanding of it, I think it is important that we do not have a man-

dated division of how the money is spent. But I have seen it with other programs. I remember the National Endowment for the Arts, a controversial issue, but part of the problem was, most of the money went to a few cities, Washington, New York, Chicago, San Francisco, Boston. So other areas did not get very much of the money.

That affects the support of that program. I saw that with Title I money. So now they mandate Title I money for rich school districts to get money, too. It does not really target economically disadvantaged. But I have been converted a little bit on this issue, that in order to get that support we need to help.

I have time, I guess, for one more question. You just briefly touched on it, and that is the new building. Would you give us an update? Is that under our budget, the new building? We have to appropriate the money? That's what I thought. It's an amazing development, but where do we stand? I know the costs have gone up, the time line.

Dr. KIRSCHSTEIN. The funds for what will probably be an increase are not noted in the budget for fiscal year 2002 or 2003. There are funds which have been appropriated already for 2002 and construction is continuing.

We are working with the Department and the Office of Management and Budget to find solutions for that. As soon as they have been found, we will come to the Committee.

Mr. MILLER. Has the completion been delayed because of it?

Dr. KIRSCHSTEIN. There will be some delay.

Mr. MILLER. When do you expect to move in it?

Dr. KIRSCHSTEIN. Probably in the late spring of 2004.

Mr. MILLER. Thank you very much.

Mr. REGULA [resuming chair]. Mr. Jackson.

Mr. JACKSON. Thank you, Mr. Chairman.

NATIONAL CENTER ON MINORITY HEALTH DISPARITIES

Welcome, Dr. Kirschstein, and thank you for your testimony.

I have a series of questions, Mr. Chairman, that I am going to submit for the record. But I do want to ask four of Dr. Kirschstein this afternoon. Dr. Kirschstein, I was extremely pleased to note that the new National Center on Minority Health and Health Disparities made its initial awards for research endowments to several minority health professions institutions last year. I look forward to working with you and Dr. Ruffin to ensure that the research endowment program is formally established as a multi-year initiative.

I am, however, concerned that other provisions of the legislation authorizing the new national center have not yet been addressed. As you know, and I hope that all the directors who are present are listening to this very clearly, because I am going to be, over the course of their testimonies before this Committee, asking them a series of questions about their understanding of this legislation. As you know, the authorizing legislation provided comprehensive authority for the Director of the National Center to coordinate health disparities research at NIH. The law also calls for the establishment of an advisory council on minority health and health disparities.

In addition, the law provides for development of a comprehensive plan and budget for all NIH minority health research, that is, all of it, which is to be coordinated and approved by the Director of the National Center. I am hoping, Dr. Kirschstein, that today or soon you can provide the Subcommittee with an update on the progress that has been made in these areas. I guess that's my first question.

My second question, in recent budget documents, NIH has identified a total of $2.4 billion that was directed towards health disparities research at the various institutes in fiscal year 2001. This amount included $74 million dedicated to the Office of the Director. It is my understanding that none of these additional dollars, $74 million, were provided to the National Center for Minority Health and Health Disparities. I am hoping that you could answer this question as well.

Given that the primary responsibility for health disparities at NIH lies with the National Center, do you think that the Center could have benefitted from some of those dollars? Moreover, do you believe that the National Center could benefit from any future funds provided by your office for health disparities research at NIH? And lastly, Dr. Kirschstein, the fiscal year 2002 budget justification for NIH contained a chart which is supposed to be attached to something—oh, it's attached to my document, I'll share it with you shortly—which showed that NIH is spending about $2.4 billion annually, or roughly 10 percent of its budget, on health disparities research. I am hoping you can provide a detailed breakdown of these dollars for the hearing and for the record.

Thank you, Dr. Kirschstein, and thank you, Mr. Chairman.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH

Health Disparities
(Dollars in millions)

Participating ICs	FY 2001 Actual
NCI	$350.3
NHLBI	218.2
NIDCR	19.0
NIDDK	126.0
NINDS	33.7
NIAID	579.5
NIGMS	149.8
NICHD	242.9
NEI	36.3
NIEHS	30.4
NIA	73.3
NIAMS	38.8
NIDCD	4.5
NIMH	160.0
NIDA	26.9
NIAAA	33.4
NINR	28.9
NHGRI	10.2
NCRR	64.9
NCCAM	12.5
NCMHD	125.1
FIC	1.1
NLM	3.0
OD	2.8
NIH*	2,371.5

*May not add due to rounding.

Dr. KIRSCHSTEIN. Thank you, Mr. Jackson. I will provide things in detail for the record.

There are two things that might be discussed. I believe the legislation calls for there to be oversight and coordination by the Director of the National Center in cooperation with the Director of the National Institutes of Health. Secondly, in terms of the $74 million you were talking about, when that money was allocated by me, $20 million of it went to the then-Office of Research on Minority Health. I think, if you will, I'd like to ask Dr. Ruffin to expand a bit on some of those answers, and particularly on the endowments.

Dr. RUFFIN. Thank you, Dr. Kirschstein, and thank you, Mr. Jackson.

As you know, P.L. 106–525, which established the Center, the National Center on Minority Health and Health Disparities, had a number of statutory mandates that were listed. Prominent among those was a strategic plan, the endowment, the establishment of a loan repayment program, and also health disparities centers of excellence.

On January 16th, I think, the Center celebrated its first year as a national center. I am very pleased to say to you that in each one of those categories that were listed, each one of the statutory mandates that were listed, that the Center, along with all of the ICs at NIH and certainly with the help of Dr. Kirschstein, have now established each of those programs.

The strategic plan is now in place and has been turned over to Dr. Kirschstein for her review and subsequent review by all of the ICs, and then submitted to the Secretary for his approval and review. Then from there of course to the Congress.

The endowment program particularly includes the 736 institutions, institutions that were statutorily mandated by HRSA. We are working collaboratively with HRSA to establish the endowment program in those institutions. In fiscal year 2001, twenty institutions around the country were officially designated as 736 institutions. Of those twenty, about sixteen of them actually applied for the endowment program. Of that number, I think about five of those institutions received awards. There is a possibility that two other institutions may be awarded as well.

NCMHD ADVISORY COUNCIL

Mr. JACKSON. Dr. Ruffin, let me back up for a moment. I know my time is going to draw near.

I remember questioning Dr. Varmus before this Committee several years ago. Dr. Varmus, I guess by the Cancer Institute's advisory committee, was given some advice for which he accepted the advice and moved forward. My understanding, after having questioned Dr. Varmus, that the history of advisory councils when they offer the director advice, they take the advice and then essentially accept the advice.

But when the advisory council offers advice on the establishment of the Center, which I provided documents to this Committee, Dr. Varmus rejected the advice. Dr. Varmus—well, he rejected the advice.

So when I asked the question about the advisory council and the establishment of it beyond the comprehensive strategic plan and

the creation of that advisory panel, that if that advisory panel gives the director or the acting director of the NIH specific information or advice regarding minority health and health disparities, that the director relies heavily upon the advice of that advisory council, pan-NIH, across the entire spectrum of NIH.

So what is the status of the creation of that advisory council that is supposed to advise the director of NIH specifically about health disparities and health research disparities across NIH? And that's an important question, because there is precedent for directors and acting directors of NIH to follow the advice of their council.

Dr. RUFFIN. As I understand it, the membership of the advisory council is now being finalized. We are certainly planning and hoping that that advisory council will be in place by May, and that the National Center will have its first advisory council meeting during that time.

Mr. JACKSON. Thank you, Mr. Ruffin. Thank you, Dr. Kirschstein, Mr. Chairman.

ORAL CANCER

Mr. REGULA. A few questions. First, one for Chairman Bill Young, who is sorry he could not be here.

Chairman Young met in Florida with several dentists last week, and the topic of oral cancer came up. He was surprised to learn that one death occurs every hour in the United States due to oral cancer. He wondered if you could tell us what NIH is doing to work on early diagnosis and prevention of oral cancer.

Dr. KIRSCHSTEIN. The NIH, and particularly the National Institute on Dental and Craniofacial Research, is expanding its program. Dr. Larry Tabak, the Director, would like to answer that question.

Dr. TABAK. Thank you, Mr. Chairman, for the opportunity to outline for you some of NIDCR's efforts. Head and neck cancer remains a disfiguring disease associated with a high mortality rate, as you have noted. Each year about 30,000 new cases are diagnosed.

Mr. REGULA. If I can interrupt, is it usually associated with tobacco? Either snuff or pipe or whatever?

Dr. TABAK. Yes. Certainly two factors have been noted, tobacco being one, and alcohol use being the other. As a result, about 8,000 Americans will die each year from these diseases.

About 90 percent of these cancers are so-called squamous cell carcinomas. These are cancers of the cells that line the inside of your cheeks, the floor of your mouth, your pharynx, your lips and the tongue. The incident rates for African-American males are about 40 percent higher than white males. Yet the rates for African-American and white women are comparable. The overall survival rate is very much dependent upon the time of detection. So when detected at the earliest stages of the disease, the survival rate is about 80 percent. But if you are detected in the late stages, the survival rate drops to 22 percent.

NIDCR has made significant investments in research in this area. In particular, the step wise progression of these types of cancer has been intensely studied. At each stage, the affected cells take on a unique signature. By recognizing what that signature is,

you will begin to have the ability to detect the earliest stages of this disease at a time when the cell seemingly appears normal.

As a result, investigators supported by NIDCR have been able to develop a test using the genetic material from cheek cells that have sloughed off into your saliva. It turns out that those cells have a signature identical to the cancer. So what this provides is a basis for reliable non-invasive tests using saliva as the medium to analyze.

Obviously we are working very hard toward enhancing the translation of the fundamental scientific discoveries. Together with the NCI, we will be funding specialized programs of research excellence in head and neck cancer this fiscal year. We also currently support five state model programs for oral cancer prevention and early detection. These are located in Florida, Illinois, Michigan, New York and North Carolina. These are community based programs in which incidence and mortality rates are being defined for each state. Risk factor knowledge is being examined, both by practitioners as well as the subjects in the community, and health professional practices will also be determined.

It is our hope that these types of studies will provide the basis for the interventions that will be necessary and can be uniquely tailored for the individual states that are represented.

Mr. REGULA. With a little bit of luck, can you get early detection and is it treatable?

Dr. TABAK. Yes. In fact, if you detect this disease at its earliest stage, the survival rates are over 80 percent.

Dr. KIRSCHSTEIN. Mr. Chairman, I might add, for what Mr. Miller was talking about before, that this is a very clear example of research being done on cancer and its related activities in the Dental Institute and the collaboration that you heard about is a very important part of it.

GRANT APPLICATION PROCESS

Mr. REGULA. It seems to me, something else, procedurally to do the research, a university or a college or like Sloan Kettering or whatever, they submit a proposal to you to do research in a field, am I correct?

Dr. KIRSCHSTEIN. Yes, sir.

Mr. REGULA. And they will define the ways in which they hope to do this and what result they might achieve?

Dr. KIRSCHSTEIN. They will predict what might be the result, or they will pose a question about what might be the options of what they are finding. Sometimes if the area is ready for an expansion of research activity, rather than relying completely on investigators proposing to us what to do, the institute involved will issue a request for a grant application or in some cases, contract proposals inviting a series of applications to be submitted in that area. Then we will choose among them, based on the peer review system.

The institute has then in that case probably decided about how much funds should be available for that particular area of research. I am sure this may have been something that Dr. Tabak did in the case of the Dental Institute. So they are anticipating a group of applications coming.

Mr. REGULA. And to determine what kind of an application you are going to seek, have you identified something that would benefit from research in, let's say, cancer or Parkinson's, whatever the case might be?

Dr. KIRSCHSTEIN. It depends on the stage at which you issue this. If it is clear that what is the need is to study the basic cancer cells and how you can develop a test to allow detection sooner, then that is what the request for applications will outline. If the institute feels that the field is further along and would benefit most by the development of a therapy, then it will issue something about that. If it thinks it requires increasing the need for being able to do images of the area involved, it will work on that. So it very much depends on the stage of the research.

Mr. REGULA. What kind of an institution initiates, let's say that Mayo Clinic decides it would be real profitable to do some research on juvenile diabetes. Could the institutes, clinics suggest to NIH, we think that there ought go be research in this field, and this is why?

Dr. KIRSCHSTEIN. Absolutely. Sometimes an investigator-initiated research effort, or sometimes because they come together with others in a conference room or are discussing the issue from which arises a series of recommendations that the various institutions out there pick up, or the institute picks up and says to a large number of institutions, we think this is a fruitful area. If you wish to work in this, let us know.

Mr. REGULA. Can research lead you down a path you hadn't even anticipated when you started out?

Dr. KIRSCHSTEIN. Absolutely. Yes. I can give you one very beautiful example. I have used this for many, many years. But it is a very nice, simple example. An investigator who asked the question as to whether or not the growth of bacteria would be inhibited by electrical fields. So he set up a series of petri dishes with bacteria growing on them, and put electrodes on and sent electricity through the dish. In only one dish was there inhibition. What was the difference?

As he looked into it, that dish had a platinum electrode in it. The others were other metals. There was enormous inhibition of the growth of bacteria. He repeated it until he found it was really true. Immediately, serendipitously, he decided maybe this is really more than just bacteria being inhibited. That led fairly rapidly to the most important new anti-cancer drug, cisplatin.

Mr. REGULA. Well, I guess that proves the value of research. [Laughter.]

Dr. KIRSCHSTEIN. Yes, sir.

RESEARCH GRANTS

Mr. REGULA. Is a normal project about three years?

Dr. KIRSCHSTEIN. The average length of a research grant these days, is four years. They can submit requests for anywhere from three to five years, and the average is four years. That was actually something that has been true since we had a discussion with this Committee back in 1993, as I recall, when there was concern that there were a number of grant applications that were going on

for five years and there were young people who could not get into the system.

It was suggested by this Committee in its report to us that the average length be about four years.

Mr. REGULA. When you make a grant, you know it is going to be over four years, I assume you make the payout over a four year period to the grantee.

Dr. KIRSCHSTEIN. That is correct.

Mr. REGULA. Do you have obligated funds that you grant Institution X, a four year research project, do you obligate funds in case we don't appropriate enough new money?

Dr. KIRSCHSTEIN. No, sir. We obligate funds for one year, but we make a commitment to that institution and that investigator that there are funds provided in the budget for the next years. So you will see in the mechanism table that we submit for NIH as a whole and that each institute submits under research grants, you will see a line item for the total number of grants we anticipate paying for the year.

That is divided into several parts, but the two major ones are the new and competing grants; that is new money that we are requesting and the Administration is requesting for that particular year. Then there is money that we are requesting in a commitment base that has carried over from the previous year for those grants to which we have assured the investigator, that because he or she has met the requirements of peer review and the importance of the work and has passed through council review, that we will pay as non-competing grants.

Mr. REGULA. I don't want to create any shock waves, but if we were to say, flat fund after the five year commitment, flat fund, would you be able to meet those obligations, for grants that are already in process?

Dr. KIRSCHSTEIN. In flat funding, yes, because the commitment would be almost enough. Now, Mr. Obey raised the issue of perhaps it would not quite be enough. But I believe it would be, and I think my budget people have told me that.

Mr. REGULA. So you would be comfortable?

Dr. KIRSCHSTEIN. There might not be any money for new grants but we actually were doing a modeling which said there would be funds.

Mr. REGULA. In other words, obviously you couldn't go to new ones.

Dr. KIRSCHSTEIN. We might be able to, depending on what one means by flat funding. Because the competing grants go for four years. So the ones that come to the four year end will turn into the non-competing grants for four years. They will create new money which is generated, so flat funding will have a certain amount of new money in it.

Mr. REGULA. Do your directors work with the grantees during the process of the work they are doing?

Dr. KIRSCHSTEIN. The staff do work closely with them, it's an ongoing dialogue.

CLINICAL TRIALS

Mr. REGULA. When you get a grant completed, and the results are back, is that information published?

Dr. KIRSCHSTEIN. Almost always.

Mr. REGULA. So the general public, the scientific community and the medical community, has access to all this?

Dr. KIRSCHSTEIN. First of all, they have access to all funded, information about funded grants through a web base that we have. It's called CRISP. If I'm not mistaken, the abstract and what is going on and the progress, for every grant that is funded, is available to anybody who wishes it.

A lot of it is in scientific terms and it is most useful to the scientists. But scientists make progress in their work as they go through the period of the four years. And they will publish scientific papers along the way. If there is a discovery that is important, that will be translated into language that ends up in the press or ends up in a story that is accessible to the public.

Mr. REGULA. So a four year grant would have a flow of information during the period of time which would be on your web site?

Dr. KIRSCHSTEIN. Exactly.

Dr. BALDWIN. At the moment, it is the abstract of the project.

Dr. KIRSCHSTEIN. Yes, but that's fine.

Dr. BALDWIN. It would also include updated information.

Mr. REGULA. But the information is available?

Dr. KIRSCHSTEIN. Yes, absolutely.

Mr. REGULA. So if somebody is following the progress of this particular project, they could do so.

Dr. KIRSCHSTEIN. Furthermore, all of the clinical studies that are being performed with NIH money and perhaps with other money as well, are available to the public through a data base that NIH has up on the web called clinicaltrials.gov. Anybody who is seeking information about the most up to date treatment of certain diseases, (it is funded through the National Library of Medicine), can go to that data base.

GOVERNMENT PERFORMANCE REVIEW ACT

Mr. REGULA. I understand that OMB is working on the development of some basic research metrics. Tell the members of the Committee more about this. Translate that into layman's language.

Dr. KIRSCHSTEIN. The Government Performance Review Act requires that all Federal agencies develop a performance basis for determining how efficient and effective they may be. That is required on a yearly basis. Doing this for research which is not done in increments of one year, but is done over four, five, maybe more years, because it is a continuum, is a daunting task. But there are some aspects of it that can be done, and we are working with the Office of Management and Budget in development of a plan that might be able to do something about this, somewhat better than perhaps we might think.

Mr. REGULA. So this is ongoing. Will it be ready for the 2003 grant proposals?

Dr. KIRSCHSTEIN. We have already done an assessment of 2001 and 2002 by looking at our entire research portfolio and dividing

it into areas such as those that are related to prevention and those that are related to therapeutics and so forth. We have had two such reviews performed by outside groups, members of the advisory committee to the director, as well as members of a second advisory group that we have, the Council of Public Representatives. We send them a number of books that are about this high describing all the accomplishments that the institute directors have selected them for that particular year. Usually it is not just—one can't divide it up into exactly what was done in one year. But there is a history. They go through them.

The groups that have done this for the past two years have been enormously impressed by the accomplishments.

Now, for 2003, we will be working with the OMB on some changes.

CHANGE IN MEDICAL EDUCATION

Mr. REGULA. Last question. Obviously you graduated from medical school a couple of years ago. How has medical education changed? You have seen it over a pretty long period of time. And a follow-up question to that is, do the NIH activities impact on medical education in the universities, colleges and so on across the Nation?

Dr. KIRSCHSTEIN. I think medical education has changed, because the science has changed. It was a much less complicated curriculum, I think, back in 1947 when I started medical school.

I think there has been an attempt by the medical schools to change that curriculum. They are always thinking about how to make it better. There are some things I know they feel they need to change in ways that they have not yet done. There certainly is more education in the basic sciences, because there is more to learn. There are medical schools now as the one that you have in Rootstown that are based in community-based hospitals as opposed to the large, more academically oriented hospitals. I think there is an emphasis on doing some things that allow doctors to treat patients more at the bedside.

There are some things that are not taught in medical school that we feel researchers need to know. For that reason, we at NIH have developed a curriculum award for people who have gone through medical school who are in academic settings, want to do research, to learn about the ways one does clinical research, how to do a statistical analysis of a clinical trial, how to provide information that is needed the Food and Drug Administration, for an investigational new drug application, in order to be allowed to do the study. How to obtain, if needed, informed consent from a patient. How institutional review boards for clinical research do their work.

So this is a field that is constantly evolving.

Mr. REGULA. Your activities at NIH do spill out into the medical education community.

Dr. KIRSCHSTEIN. In indirect ways as well, Mr. Chairman. Because of the importance of research in those medical school environments, NIH staff go and lecture and talk at those schools. Many of them have adjunct appointments.

Mr. REGULA. They go to the schools to lecture?

Dr. KIRSCHSTEIN. Yes.

Mr. REGULA. That's great.

Dr. KIRSCHSTEIN. We are not permitted, except in one instance which I will come to in a moment, to provide for support of the education of physicians who are training solely to be practitioners. We have one program where we are training people to be physicians and also researchers, the medical student training program, MSTP, for the double M.D.-Ph.D degree, which can support tuition. We can train and we do do a good deal of training of post-M.D. individuals in learning the craft of research in the specialties. We can even support funds for their tuition for special courses.

Mr. REGULA. Well, thank you. This has been a great hearing. You have all been excellent. I want to thank you for your wonderful service to the Nation.

Dr. KIRSCHSTEIN. Thank you, sir.

Mr. REGULA. And I want to tell you, you are a powerful argument against early retirement. [Laughter.]

Dr. KIRSCHSTEIN. Mr. Wicker said earlier, I think you were not here, Mr. Chairman, that he thought I had announced my retirement. I have not. [Laughter.]

Mr. REGULA. Whenever.

Dr. KIRSCHSTEIN. I am going to go back, I think, the job that I have rightfully held and is being held by the acting, the Deputy Director, unless the Director does not want me. Thank you very much.

Mr. REGULA. Thank you. The Committee is adjourned.

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

POST-DOUBLING STRATEGIES

Mr. Regula: In response to questions at last year's hearing regarding how NIH will manage its research portfolio in the post-doubling years when the agency goes back to receiving much smaller increases, you stated that NIH planned to convene groups of Institute Directors over the summer to consider what policies NIH should implement to ease the transition. What were the results and recommendations of these meetings?

Dr. Kirschstein: Strategies for handling grants funding in the post-doubling years were discussed at the Director's Forum in September of 2001, but no specific recommendations were made. A strategy incorporated into the FY 2003 President's Budget is the expenditure for large one-time infrastructure costs which provides great benefit by enabling the development of research facilities to mirror the astounding growth and development of related technologies. Budget plans benefit from such one-time costs because of the absence of financial commitment in future years. This strategy would enable the NIH to maintain commitments for non-competing grants and to continue supporting approximately the same number of new and competing research project grants in FY 2004. Should one-time costs in FY 2004 be directed to high priority or emerging areas as was the case with bioterrorism in FY 2003, there could be significant effect on the NIH grant portfolio.

OUTYEAR EFFECTS OF FY 2003 REQUEST LEVEL

Mr. Regula: What are the advantages and disadvantages of slowing down the spending rate? Would it make year six and beyond more manageable?

Dr. Kirschstein: Any reduction from the requested level in FY 2003 would hinder the incorporation of the highest technological standards possible into our nation's research facilities, and likely would result in delays and lost funding opportunities for many worthwhile projects proposed by our nation's research scientists.

PREPARING RESEARCH COMMUNITY FOR FUTURE NIH BUDGET

Mr. Regula: The focus over the last five years has been on the appropriation for NIH and reaching that bottom line funding level. Are we putting ourselves in a position in fiscal year 2004 where the level of new and competing grants will be dramatically lower than the past five years thereby creating a panic among researchers?

Dr. Kirschstein: There will always be some concern in the scientific community if the NIH budget is not substantially increased. However, the one constant factor in changing budget situations has been the NIH peer review system. It is the cornerstone of the scientific enterprise and it assures researchers, and the public, that the most competitive, highly meritorious projects will be funded. The scientific community understands that there are many pressures on the federal budget and I hope that they

understand that we will look very carefully at how we work within the budget and yet support the overall scientific enterprise. That said, I believe that NIH has developed a budget planning strategy in FY 2003 that would enable us to maintain approximately the same number of new research project grant opportunities in FY 2004. Should one-time costs in FY 2004 be directed to high priority or emerging areas as was the case with bioterrorism in FY 2003, there could be significant effect on the NIH grant portfolio.

Mr. Regula: What are you doing to prepare the research community for smaller budget increases?

Dr. Kirschstein: We have reinforced to the research community the important principle that NIH supports the best science through peer review. The one constant factor in the changing budget situations has been the NIH peer review system. It is the cornerstone of the scientific enterprise and it assures researchers, and the public, that the most competitive, highly meritorious projects will be funded. The scientific community understands that there are many pressures on the federal budget and I hope that they understand that we will look very carefully at how we work within the budget and yet support the overall scientific enterprise.

ENCUMBERMENTS TO FULL FUNDING

Mr. Regula: The budget request includes language to allow for full funding of NIH grants. What prevents you from providing full funding now?

Dr. Kirschstein: The "Bona Fide Need Rule" (31 U.S.C. s1502(a)) has generally been interpreted as requiring grants to be funded incrementally, a year at a time, expect where specifically authorized differently by Congress. This law states:

'The balance of an appropriation or fund limited for obligation to a definite period is available only for payment of expenses properly incurred during the period of availability or to complete contracts properly made within that period of availability and obligated consistent with section 1501 of this title. However, the appropriation or fund is not available for expenditure for a period beyond the period otherwise authorized by law.'

In addition, in the past, the Congress had directed NIH not to fully fund grants except in limited circumstances. Between Fys 1988 and 1994, the Congress included General Provisions language in the Labor-HHS-Appropriations Bills that prohibited NIH funds, except those appropriated to the Office of the Director, from being used to forward fund or multiyear fund research project grants except in those cases where the NIH Director determined that such funding was specifically required because of the scientific requirements of a particular research project grant.

Given those prior interpretations and directions, the FY 2003 budget request seeks explicit authority to fully fund grants for budgetary as well as programmatic reasons. Although not proposed for direct use in FY 2003, having this authority would provide NIH additional flexibilities in considering options for managing our resources effectively, providing stable and predictable support for new research ideas, and funding research priorities in the outyears.

FULL FUNDING OF RESEARCH PROJECT GRANTS

Mr. Regula: You state in the budget justifications that you are in the process of analyzing whether there are grant and contract programs for which this strategy will maximize management and budgetary flexibility and once the analysis is complete, NIH will inform Congress of its findings. When can we expect to receive this information?

Dr. Kirschstein: NIH is in the process of analyzing whether there are grant and contract programs for which it is appropriate to expand the strategy of full funding the total costs to maximize management and budgetary flexibility. Therefore, the mechanism table included in the FY 2003 budget does not assume full funding of any awards, but appropriations language is included in the budget that will allow for the full funding of NIH grants. Once this analysis is complete, NIH will inform the Congress of its findings, which will be reflected in the final FY 2003 Operating Plan.

DOD COLLABORATIVE RESEARCH

Mr. Regula: The request includes $49 million to be directed towards collaborative research projects with the Department of Defense. What are the projects? Are they projects that are currently being funded by DoD? Will the research be conducted at NIH? How much will DoD contribute to these projects?

Dr. Kirschstein: In Fiscal Year 2003, the National Institutes of Health will fund the following DOD medical research that is consistent with NIH's mission: (1) research on the effects of medical technology, including Radiation Research Treatment; (2) medical free electron laser research, which could be used for medical diagnosis and therapy, and, in particular, for the debridement of wounds; and (3) HIV/AIDS research.

Yes, these projects are all currently being funded by the Department of Defense (DOD). NIH is working with DoD to finalize the details. In some cases, DOD will continue to manage and carry out its research in collaboration with NIH. In all cases, the research conducted by DOD and NIH will be enhanced through a closer sharing of knowledge and research.

OFFICE OF LOAN REPAYMENT AND SCHOLARSHIP

Mr. Regula: You began funding two loan repayment programs this year, one for extramural clinical researchers and one for pediatric researchers. Both programs are designed to increase the number of clinical and pediatric research investigators. What has been the reaction in the medical and research community to these programs?

Dr. Kirschstein: The Loan Repayment Program for Clinical Researchers and the Loan Repayment Program for Pediatric Researchers have generated considerable interest in the medical and research communities. We have received a total of 692 applications this fiscal year, and we expect to provide these to the appropriate NIH Institutes and Centers for review during the first week in April 2002.

Mr. Regula: Who is eligible to receive a loan repayment and what are the requirements for a program participant?

Dr. Kirschstein: There are currently nine different Loan Repayment Programs available from the NIH for biomedical investigators and physician scientists.

The general eligibility criteria for the Loan Repayment Programs require that an individual: 1) be a U.S. citizen, national, or permanent resident of the United States; 2) hold a qualifying doctoral degree; 3) perform qualifying research supported by the NIH, a foundation, a professional society, or a non-profit organization, or as an employee of the NIH; 4) have total educational loan debt that equals or exceeds 20 percent of their annual income; 5) agree to perform two years of research service in approved research; and 6) conduct research for which funding is not prohibited by Federal law, regulation or DHHS/NIH policy.

Some of the Loan Repayment Programs have additional eligibility criteria. For example, applicants for the Clinical Research LRP for Individuals from Disadvantaged Backgrounds must demonstrate that they are from a "disadvantaged background," and applicants for the Contraception and Infertility Research Loan Repayment Program must agree to conduct research at a specific extramural site that has been approved by the NIH.

Mr. Regula: Are you confident you are reaching all potential recipients in order to achieve the intended goals of the program?

Dr. Kirschstein: Information about the Loan Repayment Programs has been widely distributed. NIH officials have made numerous presentations about the programs at educational institutions and professional associations, and notices have been placed in the *NIH Guide to Grants and Contracts* and our Internet home page (www.lrp.nih.gov). There have also been articles about the Loan Repayment Programs in several journals, including the *New England Journal of Medicine,* the *Archives of Pediatrics and Adolescent Medicine*, and *Gastroenterology*. The far-reaching dissemination of

information about this program is evidenced by the large number of applications submitted, as well as the wide geographical distribution of the applicants - we have received applications from individuals in 46 states, the District of Columbia, and the Commonwealth of Puerto Rico.

DESCRIPTION OF FOUNDATION OPERATION

Mr. Regula: The National Institutes of Health Revitalization Act of 1993 authorized the creation of a National Foundation for Biomedical Research. Describe the operation of the Foundation in further detail.

Dr. Kirschstein: In 2000 the Congress provided for a change in name from the National Foundation for Biomedical Research to the Foundation for the National Institutes of Health to more accurately reflect its mission to support the programs of the NIH. The Foundation is incorporated in Maryland as a 501(c)(3) nonprofit corporation and is completely independent of the NIH, i.e., no NIH employees serve on the Board of Directors and no NIH employees occupy decision-making positions on the Foundation staff. The Foundation has a Board of Directors consisting of 12 individuals, including distinguished scientists (two of whom are Nobel Laureates), members of industry, and noted philanthropists. The Foundation's staff currently consists of six full time positions.

The Foundation's staff works closely with NIH staff and potential donors to identify or develop programs at NIH to be supported with outside funds. For example, the Foundation has recently raised $7.5 million for the Family Lodge, a facility similar to the Children's Inn, that will provide a place to stay on campus for families of adults enrolled in clinical studies at the NIH Clinical Center. Construction will begin this summer. Another program that began in this manner is the Clinical Research Training Program, a program to expose third year medical and dental school students to clinical research on the NIH campus. The goal is to increase the number of physicians and dentists trained in the conduct of clinical research. The Foundation found a donor, the Pfizer Corporation, with a strong interest in supporting this program. Other programs, like the Sallie Rosen Kaplan Fellowship for Women Scientists in Cancer Research, have been the result of donors approaching the Foundation to find an appropriate way to make a gift to NIH. The Foundation worked with NIH staff to develop a program in response to this gift. Other programs have involved collaborations among the Foundation, NIH institutes, and private industry. For example, the Mouse Genome Sequencing program was a collaboration among the Foundation, the National Institute for Human Genome Research, and several pharmaceutical companies to sequence the mouse genome and place it in the public domain for all to use. This program was completed in 2001.

FULFILLMENT OF FOUNDATION EDUCATIONAL MANDATE

Mr. Regula: When the Foundation was authorized, the expectation was that it would be a source for educational courses and related material for NIH. How has the Foundation fulfilled this mandate?

Dr. Kirschstein: The Foundation supports a number of educational programs at the NIH. The following are some of the most important. The Clinical Research Training Program (CRTP) provides a year of training for third year medical and dental students in the conduct of clinical research. The goal of this program is to increase the number of physicians and dentists engaged in clinical research. The Biomedical Engineering Summer Internship Program (BESIP) brings undergraduate students enrolled in biomedical engineering programs to the NIH campus for a summer to expose them to the biomedical engineering programs of NIH. The National Coalition for Health Professional Education in Genetics trains health professionals in the most recent advances in genetics. The Pain and Palliative Care programs train health professionals in the most recent techniques for alleviating pain. The Multilateral Initiative on Malaria trains foreign physicians and health workers in how to treat and prevent malaria. In addition to these programs, the Foundation also supports a number of individual fellowships at specific institutes.

USE OF FOUNDATION BUDGET

Mr. Regula: Since 1996, the Foundation has collected donations of $18.7 million and had program expenses of $10.7 million. How has this $10.7 million been used? What are the plans for the remaining $8 million?

Dr. Kirschstein: The following table displays the Foundation's program expenses from 1998 through 2000. Note: there were no program expenses for 1996 and 1997 because the first Foundation programs did not begin until 1998.

	(Dollars in millions)			
	1998	1999	2000	Total
Fellowships & Training	$471,672	$647,041	$694,508	$1,813,221
Memorials, Awards & Events	30,336	19,299	91,743	141,378
Capital Projects		17,438	420,235	437,673
Research Partnerships		-	8,360,619	8,360,619
	502,008	683,778	9,567,105	10,752,891

The Capital Project for which the Foundation is raising funds is the NIH Family Lodge, a facility that will provide housing for the family members of adults enrolled in research protocols at the NIH Clinical Center. We are pleased to announce that in 2002 the Foundation succeeded in raising the $7.5 million needed. Construction will begin this summer. The major research partnership was the Mouse Genome Sequencing

Project, a collaboration between the Foundation, the National Human Genome Research Institute and several industry partners to sequence the mouse genome and place it in the public domain for all to use. This project was successfully completed in 2001.

Most of the remaining $8 million will be used to construct the NIH Family Lodge. Additional funds will also be used for the Clinical Research Training Program, which has been supported by a generous donation from the Pfizer Corporation, the Biomedical Engineering Summer Internship program, two programs to increase the research training opportunities for women, and several other smaller programs. I should point out that the Foundation, following accepted accounting practices for nonprofit organizations, records the value of pledges in the year the pledge is made. Typically, large pledges may be paid to the Foundation over several years. Thus, while the Foundation does show a balance of $8 million, it did not, at the end of 2000, actually have all of that $8 million in hand.

FOUNDATION APPROPRIATION

Mr. Regula: Was the intent of the authorization that the Foundation should receive an appropriation in perpetuity?

Dr. Kirschstein: The Foundation has a permanent yearly authorization in the amount of $500,000. The current legislation does not mention a time limit on appropriations made pursuant to this authorization. However, the Foundation has made progress in becoming self-sufficient. In the early years, the Foundation was totally reliant on the federal appropriation for its operations, but in Fiscal Year 2000, the federal appropriation supported only 59% of the Foundation's operating expenses.

Of the $18.7 million the Foundation has raised in contributions, $18.4, or 99%, has been raised in what are called "restricted" contributions, contributions that can only be used to support specific NIH programs. Approximately $300,000 has been raised in "unrestricted" contributions that can be used for the general support of the Foundation's operations.

IMPLEMENTATION OF STEM CELL RESEARCH POLICY

Mr. Regula: Are you satisfied with the progress of implementation of the President's stem cell research policy?

Dr. Kirschstein: Yes. My staff have worked diligently to establish the Registry of acceptable cell lines and make it available on our website. We have taken steps to relax the winter receipt date and to develop a tracking system for projects using stem cells. We have ensured that questions from the research community are addressed in the section on Frequently Asked Questions on our website and many ICs have publicized their interest in receiving applications for either administrative supplements or new grants or both for which stem cell technology is used. These cell lines were developed

with private funding and some of the sources have commercial interests. While the NIH interest lies with the basic science applications, there have been some challenges for sources as intellectual property issues are worked out. Because human embryonic stem cells can be difficult to work with, we are supporting training initiatives. These will not result in the immediate flow of research, but will strengthen the overall scientific portfolio in time. Finally, because many of the providers of stem cells were not already prepared to scale up to meet the likely demand from the scientific community we are entertaining requests for funding to help enhance their infrastructure so that they can meet those needs. The first such awards will be made shortly.

NEW INVESTIGATORS

Mr. Regula: Update the tables that appear on pages 723 and 724 of last year's hearing record that shows the number of applications from applicants who have never submitted a research project grant earlier to include fiscal year 2000 actual and the fiscal year 2001 estimate.

Dr. Kirschstein: The information is provided below:

NIH R01 Applications from Applicants Who had never submitted a Research Project Grant (RPG) earlier

Fiscal Year	Reviewed	Award	Success Rate
1995	1875	266	14.2%
1996	1576	247	15.7%
1997	1536	294	19.1%
1998	1632	353	21.6%
1999	3441	756	22.0%
2000	2774	610	22.0%
2001*	3105	605	19.5%

*FY 2001 data are estimates

NIH R01 and R29 Competing Applications
Investigators without prior Competing RPG Award

Fiscal Year	Reviewed	Award	Success Rate
1995	7547	1413	18.7%
1996	6928	1371	19.8%
1997	6719	1503	22.4%
1998	6490	1500	23.1%
1999	7301	1623	22.2%
2000	7147	1630	22.8%
2001*	7697	1741	22.6%

*FY 2001 data are estimates

FTE CEILINGS

Mr. Regula: Update the table on page 723 of last year's hearing record that shows NIHs FTE level to include fiscal year 2001 actual and fiscal year 2003 estimates.

Dr. Kirschstein: The information is provided below:
This table excludes adjustments for Intra-Departmental transfers.

	FY 96 Actual	FY 97 Actual	FY 98 Actual	FY 99 Actual	FY 00 Actual	FY 01 Actual	FY 02 Estimate	FY 03 Estimate
Ceiling FTE	15,099	15,103	15,159	15,307	16,005	16,509	17,443	17,668
Undistributed FTEs						4		
CRADA FTEs	15	29	21	22	17	12	28	28
Total	15,114	15,132	15,180	15,329	16,022	16,525	17,471	17,696

DIRECTOR'S DISCRETIONARY FUND

Mr. Regula: Identify the uses for the Director's discretionary fund for fiscal year 2001. Have any funds been committed from the fiscal year 2002 discretionary fund at this time?

Dr. Kirschstein: The information is provided in the following table:

FY 2001 Director's Discretionary Fund

	$9,874	Available
NIGMS	3,800	Protein Data Bank
NCI	500	Mideast Cancer Consortium
NINDS/ NIAID/ NIA	4,885	Bovine Spongiform Encephaly Research Projects
NICHD	500	Autism Research Project
NCRR	50	Support to Houston Area- Institutions following Tropical Storm Allison
OSP	139	Support for Stem Cell Meetings
Total DDF	9,874	

FY 2002 Director's Discretionary Fund

	$10,000	Available
NHGRI	500	Haploid Map
NICHD	5,000	Pediatric Research Initiative
Total DDF	5,500	

FTES

Mr. Regula: Update the table provided last year showing NIH FTE's broken down by each ICD and central services to include fiscal year 2001 actual and fiscal years 2002 and 2003 estimates.

Dr. Kirschstein: The information is provided below. This table excludes adjustments for Intra-Departmental transfers.

National Institutes of Health
Full-Time Equivalent Employment (FTE)
Total by Institute

IC	FY 95 Actual	FY 96 Actual	FY 97 Actual	FY 98 Actual	FY 99 Actual	FY 00 Actual	FY 01 Actual	FY 02 Estimate	FY 03 Estimate
NCI	2,219	2,180	2,250	2,294	2,393	2,794	2,979	3,150	3,188
NHLBI	822	834	829	840	847	865	868	878	877
NIDCR	314	301	281	280	291	295	290	300	299
NIDDK	570	545	552	572	585	599	627	645	642
NINDS	650	620	607	595	587	597	589	618	616
NIAID	1,040	1,006	1,029	1,067	1,062	1,114	1,177	1,295	1,524
NIGMS	172	168	171	165	165	171	170	179	178
NICHD	481	485	493	516	529	542	562	576	574
NEI	240	233	225	217	212	221	233	248	247
NIEHS	650	640	659	677	690	720	734	772	769
NIA	426	411	399	392	388	384	395	445	444
NIAMS	147	157	160	169	174	188	209	212	212
NIDCD	125	126	133	142	133	134	150	155	155
NIMH	844	829	833	789	731	711	737	787	785
NIDA	360	364	356	360	359	368	370	384	382
NIAAA	220	226	219	216	222	217	231	262	261
NINR	44	41	37	40	39	42	40	55	55
NHGRI	173	187	197	217	217	246	275	275	278
NIBIB	--	--	--	--	--	0	0	21	30
NCRR	97	93	100	94	95	103	109	119	118
NCCAM	--	--	--	--	7	28	45	80	80
NCMHD	--	--	--	--	--	8	9	26	26
FIC	68	72	69	67	59	64	71	79	79
NLM	575	575	574	577	602	625	656	691	688
OD	732	688	648	668	678	581	602	623	621
Central Services	4,392	4,318	4,282	4,205	4,242	4,388	4,381	4,568	4,540
Undistributed CRADA FTEs		15	29	21	22	17	4 12	28	28
Total NIH	15,361	15,114	15,132	15,180	15,329	16,022	16,525	17,471	17,696

PROGRAM EVALUATION

Mr. Regula: Also, update the table showing the dollar amounts for RMS, with the portion of RMS used for the one percent evaluation set-aside identified, as well as a separate line indicating the amount of nonRMS dollars used for the one percent set-aside to include fiscal year 2001 actual and fiscal year 2003 estimate.

Dr. Kirschstein: The information is provided below:

National Institutes of Health
Research Management and Support
FY 1991 - FY 2003
(dollars in thousands)

	Total	Program Evaluation*		
	RMS	RMS	Non-RMS	Total
FY 1991	$434,706	$31,970	$370	$32,340
FY 1992	484,327	39,093	4,181	43,274
FY 1993	493,200	39,765	3,750	43,515
FY 1994	497,886	40,892	9,893	50,785
FY 1995	506,415	36,315	19,085	55,400
FY 1996	479,746	15,103	79,395	94,498
FY 1997	479,297	10,669	78,077	88,746
FY 1998	497,121	2,843	101,602	104,445
FY 1999	540,837	2,459	121,136	123,595
FY 2000	601,471	3,446	135,912	139,358
FY 2001	719,926	3,417	188,893	193,774
FY 2002 Estimate	828,774	4,853	268,388	273,241
FY 2003 Estimate	971,499	4,847	257,350	262,197

* Includes program evaluation funds utilized within NIH itself, estimated at $7 million in FY 2002 and $7 million in FY 2003.

SPENDING BY DISEASE

Mr. Regula: Provide the traditional one-pager identifying estimated spending by disease for fiscal years 1996 through 2003.

Dr. Kirschstein: The attached table identifies the traditional one-pager on spending by disease/research area for FY 1996 - FY 2003.

NATIONAL INSTITUTES OF HEALTH
Research Initiatives/Programs of Interest

(Dollars in millions) Research/Disease Areas	FY 1996 Actual	FY 1997 Actual	FY 1998 Actual	FY 1999 Actual	FY 2000 Actual	FY2001 Actual	FY 2002 Estimate	FY 2003 Estimate
Aging Research	$904 0	$978	$1,059 5	$1,215 0	$1,468.5	$1,667.4	$1,878 2	$2,039 6
AIDS (Budget Authority)	1,410.9	1,501 1	1,602.8	1,792 7	2,004 4	2,247.0	2,515.0	2,770 0
Minority AIDS	265 7	282 3	3 17.8	359 9	394.2	439 5	487.9	535 8
Pediatric AIDS	156 6	164.7	171 4	196 0	230 4	272 8	296 8	319 1
Vaccines AIDS	205.2	221.6	148 1	182.3	232 1	269.2	339 5	422.3
ALS	10.9	13 9	15 1	17 2	15 4	27 5	30 0	32.3
Alzheimer's Disease	304.4	329.3	356 1	406 5	456.3	524.9	594 7	644 0
Anthrax Research	--	--	--	--	--	7 3	42 1	287 4
Arthritis Research	220 6	227.5	215 5	238.8	268 9	278 1	316.2	342.6
Asthma	81 6	92.5	100 9	140.4	165.0	208.8	233.7	255.6
Autism	13 0	22 2	26 9	40.0	51.7	55 8	65 1	70 5
Autoimmune Disease	--	--	327.4	393 2	435 3	495 1	563.4	608.6
Behavioral and Social Science	1,224 6	1,342 6	1,380 2	1,569 0	1,849 6	2,100 6	2,364 0	2,575 2
Bioengineering	--	485.8	577 7	697 5	633.6	692 4	792 5	960.6
Bioterrorism*	--	--	17 0	32 6	43 0	52 8	274 5	1,747 9
Brain Disorders	2,354 2	2,553.8	2,725 0	3,096.7	3,454 6	3,936.5	4,437.7	4,809.1
Cancer Research	2,570.6	2,760.7	2,940 0	3,377 3	3,854.4	4,376.4	4,929 8	5,558.8
Breast Cancer	391 6	411.2	430 1	474 7	536 0	580 9	655 2	732 3
Lung Cancer	127.8	143.4	152 4	163 0	192.0	225 6	259.2	297.0
Ovarian Cancer	42 2	48 0	49 1	65 4	78 6	90.3	104 0	118.9
Prostate Cancer	92.7	104 8	113.6	177.5	256 7	320 1	362 1	408.3
Cardiovascular Research	985.7	1,079 5	1,164.5	1,327 1	1,523 6	1,723.1	1,920 8	2,064.6
Clinical Research	--	3,998 8	4,324.4	4,920 5	5,717 3	6,433.3	7,235.7	8,037.3
Complementary and Alternative Medicine	--	42 0	88 0	116 0	170 6	212.9	247.6	269.1
Cystic Fibrosis	64.1	70.3	63 9	71 6	81 2	107 3	117 2	126 7
Diabetes Research**	298.9	319.5	387.3	457 6	540.7	688 1	781.3	845 1
Diagnostic Radiology	220 6	239 3	267.7	341.9	399 2	489.5	574 0	633 3
Emerging Infectious Diseases	77.7	90.2	134.6	158 7	184.2	222.6	382.4	1,466.6
Chronic Fatigue Syndrome	7 1	6.5	6.8	6.9	5.8	5.8	6.2	6.5
Fibromyalgia	2 2	2 3	3 1	6 4	10 7	9.5	10 6	12 3
Gene Therapy	203 5	253.2	271.1	360.8	424.2	349 4	390 1	427 4
Hepatitis - C	13 9	25 3	26 2	39 7	66 5	84 0	95 2	103 0
Hypertension	174.4	164 5	173.1	175.4	243.9	277.0	307.5	329.5
Infant Mortality/ (LBW)	316 7	313 8	353 3	383.4	399 1	448 8	506 8	561 3
Kidney Disease	190 7	196 0	206 0	236 1	277.2	320 7	367 1	399 1
Lupus	32 9	33.9	37.8	46 1	54.6	64.6	73.4	78.9
Mental Health	--	--	--	1,089 3	1,277 6	1,446.3	1,635 0	1,769.6
Multiple Sclerosis	82.8	86.4	81.9	96.3	61.9	69.8	77.5	83 9
Muscular Dystrophy	10 8	13 7	15.7	16 7	12.6	21 0	23 4	25 4
Neurosciences Research	2,293.6	2,474.2	2,637.2	3,027.3	3,341.0	3,800.7	4,305.7	4,665.0
Nutrition	438.8	453.3	494.4	553 5	665.2	755.7	859.2	942.7
Obesity	85 4	120.5	127 6	161 4	199 6	222 6	252 3	274 1
Osteoporosis	109.4	111.6	122.4	136.7	153.7	173.0	193.9	209.6
Parkinson's Disease	77 2	89.2	109 7	132 3	155 9	175 1	198 9	215.1
Pediatric Research	1,512.0	1,599.3	1,681 0	1,902.8	2,245.3	2,509 6	2,829 2	3,052.9
Polycystic Kidney Disease	8.0	6 6	7 8	11 8	15 2	18 7	21 0	22.9
Prevention	3,066 4	3,224 8	3,440 6	3,876 9	4,423 1	5,124 2	5,927 1	6,852 3
Sexually Transmitted Diseases/Herpes	102 6	120 4	123 2	136.4	144.4	167 8	190.0	208 6
Schizophrenia	111.5	110 9	135 4	200 6	241.0	276 1	312 3	338 4
Sickle Cell Disease	48.6	49.3	48 6	50.4	59.0	71.6	79.7	85.5
Sleep Disorders	76 1	84.7	98 1	119 7	123 9	148 1	166 0	178 8
Smoking and Health	137.3	287.2	320.9	353.9	379.7	448.3	503.7	554.9
Spinal Cord Injury	56 3	60 6	58 8	62 1	55 6	71 5	78 9	84 7
Stem Cell Research	--	--	--	--	--	306 0	346 C	380 2
Stroke	130.0	143.1	157.2	186.0	215.3	238 9	263.5	283.1
Sudden Infant Death Syndrome	45 9	43 7	45.3	49 3	47 6	54 2	62 0	67.5
Topical Microbicides	20 1	19.6	18.8	26.0	30.5	47.0	55.7	68.2
Transmissible Spongiform Encephalopathy (TSE)	--	--	--	--	--	24 0	24 3	26.4
Tuberculosis Research	64 1	67.2	66 1	72.8	74 4	87.3	99.4	108 4
Vaccine Development	273.1	298.3	325 1	364 1	452.4	550.9	704.3	1,195.7
Women's Health	1,831.7	1,978 2	2,085 9	2,320 1	2,697 1	2,923 1	3,390 1	4,120 4

*Amounts include $180 million appropriated to the PHS Emergency Supplemental Fund through the FY 2002 Department of Defense and Emergency Supplemental Appropriations (P.L. 107-117).

**Funds available for diabetes research (P.L. 105-33 and P.L. 106-554).

CSR STUDY SECTION REORGANIZATION

Mr. Regula: What is the status of CSR's reorganization of its study sections?

Dr. Kirschstein: During the first phase of the reorganization, the Panel on Scientific Boundaries for Review (PSBR) recommended a set of 24 Integrated Review Groups (IRGs) into which scientifically related study sections were to be clustered. Currently, CSR is conducting the second phase of the reorganization process, in which teams of expert scientists design study sections and study section guidelines for each IRG. These proposed study sections and guidelines are then posted for a 12-week public comment period.

Seven IRGs were established and populated with new study sections in 1998 and 1999; thus they will continue to function pending an evaluation process that CSR has initiated this year. Seventeen IRGs are being reorganized in the current reorganization activity. Between February and December 2001, CSR convened the first seven expert team meetings. Four more teams will meet in April 2002. The remaining six teams will meet by April 2003.

NIH staff considers all comments regarding guideline proposals and consults with additional experts as necessary. After presentation to and approval by the CSR Advisory Committee, CSRs Director will approve the final form of all guidelines. To complete logistic arrangements and ensure that applicants are fully aware of changes to study sections, new study sections will meet approximately one year after their guidelines are approved. The first reorganized study sections should meet in May 2003. The PSBR reorganization process should be completed by spring of 2005.

GRANT APPLICATIONS AND AWARDS

Mr. Regula: Update the table provided on page 738 of last year's hearing record that shows the total number of grant applications received and the number funded to include fiscal year 2001 actual and fiscal year 2003 estimates.

Dr. Kirschstein: The information you requested is reflected in the table below.

National Institutes of Health
Research Project Grants
Applications and Awards
FY 1999 - FY 2003

	Applications	Awards
FY 1999	26,407	8,566
FY 2000	27,798	8,765
FY 2001	28,368	9,186
FY 2002 (est)	30,768	9,377
FY 2003 (est)	33,216	9,854

OFFICE OF RARE DISEASES

Mr. Regula: At this time last year, you planned to create regional centers of excellence for research on rare diseases both at the NIH Clinical Center and at selected regional sites in the United States. What is the status of this initiative?

Dr. Kirschstein: The Office of Rare Diseases (ORD) plans to publish a Request for Applications (RFA) and award grants to four or five regional centers of excellence on rare diseases research this fiscal year. The ORD also initiated discussions to use the extensive intramural research investigator's network at the Warren Grant Magnuson Clinical Center at the National Institutes of Health to establish a specific initiative related to the diagnosis and research of rare diseases.

MINORITY FUNDING TABLES

Mr. Regula: Update the series of eight tables provided in last year's hearing record that shows, by Institute and Center, the programs and funding levels provided to minority institutions to include fiscal year 2001 actual and fiscal year 2002 estimates.

Dr. Kirschstein: The information is provided below.

NATIONAL INSTITUTES OF HEALTH
Research Infrastructure in Minority Institutions
(Dollars in millions)

Participating ICs	FY 2000 Actual	FY 2001 Actual	2002 Estimate
NCRR	$0.2	$0.0	$0.0
NCMHD	5.6	5.0	8.0

NATIONAL INSTITUTES OF HEALTH
Research Centers at Minority Institutions
(Dollars in millions)

Participating ICs	FY 2000 Actual	FY 2001 Actual	FY 2002 Estimate
NIAID	$2.8	$2.9	$3.3
NEI	0.0	0.4	0.4
NHGRI	0.1	0.1	0.1
NCRR	38.3	39.1	48.6
NCMHD	1.0	2.1	0.0

NATIONAL INSTITUTES OF HEALTH
Minority Biomedical Research Support Program
(Dollars in millions)

Participating ICs	FY 2000 Actual	FY 2001 Actual	FY 2002 Estimate
NCI	$3.3	$3.5	$4.0
NHLBI	2.8	3.2	3.5
NIDCR	0.1	0.1	0.1
NIDDK	2.6	1.7	3.4
NINDS	1.7	1.5	1.9
NIAID	1.1	1.2	1.4
NIGMS	71.4	81.5	91.8
NICHD	0.9	1	1.1
NEI	0.4	0.4	0.4
NIA	1.2	1.2	1.2
NIEHS	1.7	3.4	3.1
NIAMS	0.7	1.2	1.5

NATIONAL INSTITUTES OF HEALTH
Minority Access to Research Careers
(Dollars in millions)

Participating ICs	FY 2000 Actual	FY 2001 Actual	FY 2002 Estimate
NIDCR	$0.2	$0.2	$0.2
NINDS	0.1	0.1	0.1
NIGMS	24.7	28.7	30.7
NIA	0.1	0.1	0.1

NATIONAL INSTITUTES OF HEALTH
Funding to Historically Black Colleges and Universities
(Dollars in millions)

Participating ICs	FY 2000 Actual	FY 2001 Actual	FY 2002 Estimate
NCI	$2.4	$7.0	$7.8
NHLBI	4.5	5.6	6.2
NIDCR	0.5	0.1	0.1
NIDDK	3.0	2.2	2.4
NINDS	4.4	3.8	5.7
NIAID	3.6	3.8	4.3
NIGMS	34.2	33.9	36.1
NICHD	2.6	3.1	3.5
NEI	0.8	1.1	1.3
NIEHS	2.2	4.2	3.6
NIA	0.4	0.5	0.6
NIAMS	0.2	0.5	0.5
NIDCD	0.4	0.3	0.3
NIMH	3.2	5.4	6.0
NIDA	2.5	2.6	2.8
NIAAA	1.9	0.8	0.8
NINR	0.0	0.0	0.1
NHGRI	5.1	2.2	2.5
NCRR	23.6	20.6	21.6
NCCAM	0.2	0.4	0.5
NCMHD	0.0	43.6	46.7
FIC	0.9	0.9	0.9
NLM	0.5	0.4	0.4

NATIONAL INSTITUTES OF HEALTH
Funding to Hispanic Serving Institutions
(Dollars in millions)

Participating ICs	FY 2000 Actual	FY 2001 Actual	FY 2002 Estimate
NCI	$9.4	$36.0	$40.4
NHLBI	3.6	10.6	11.4
NIDCR	0.2	5.2	5.4
NIDDK	3.1	3.5	3.8
NINDS	6.8	9.0	9.4
NIAID	7.6	10.0	11.4
NIGMS	44.7	59.1	62.6
NICHD	1.2	15.2	17.2
NEI	0.8	10.2	11.6
NIEHS	2.3	4.0	2.3
NIA	0.9	15.6	17.7
NIAMS	2.0	6.0	6.8
NIDCD	0.7	1.5	1.6
NIMH	8.4	7.3	8.2
NIDA	5.0	25.3	28.5
NIAAA	6.2	8.6	9.0
NINR	0.5	2.1	0.2
NHGRI	0.3	0.8	0.5
NCRR	15.3	16.6	17.4
NCCAM	0.0	0.3	0.3
NCMHD	0.0	4.4	4.7
FIC	0.9	0.9	0.9
NLM	1.3	1.0	1.7

NATIONAL INSTITUTES OF HEALTH

Funding to Hispanic Serving Health Professional Schools

(Dollars in millions)

Participating ICs	FY 2000 Actual	FY 2001 Actual	FY 2002 Estimate
NCI	$137.2	$149.0	$166.9
NHLBI	171.7	208.8	223.1
NIDCR	12.3	18.3	19.1
NIDDK	66.1	65.3	81.5
NINDS	66.8	75.1	76.7
NIAID	106.0	113.9	130.9
NIGMS	87.4	84.0	110.0
NICHD	33.9	38.4	42.0
NEI	24.8	27.3	31.2
NIEHS	15.1	26.7	23.2
NIA	41.5	52.8	60.1
NIAMS	27.9	23.4	26.3
NIDCD	8.0	8.9	8.9
NIMH	55.4	59.0	66.7
NIDA	21.9	25.7	29.0
NIAAA	8.4	8.4	8.4
NINR	0.7	0.4	0.5
NHGRI	15.0	15.1	15.2
NCRR	51.8	53.9	55.8
NCCAM	4.9	6.6	7.3
NCMHD	0.0	0.0	0.1
FIC	2.5	3.3	3.4
NLM	4.6		

NATIONAL INSTITUTES OF HEALTH

Funding to Tribal Colleges and Universities

(Dollars in millions)

Participating ICs	FY 2000 Actual	FY 2001 Actual	FY 2002 Estimate
NIDDK	$0.0	$0.5	$0.5
NIGMS	2.4	1.8	1.9
NLM	0.0	0.2	0.2

CHIMPANZEE SANCTUARY

Mr. Regula: Provide an update on the development of a chimp sanctuary.

Dr. Kirschstein: The NIH has begun to implement provisions of the CHIMP Act. In April 2001, the HHS Secretary approved Delegation of Authority for NCRR to implement provisions of the CHIMP act and to establish a National Advisory Research Resources Council Working Group for Interim Sanctuary Standards of Operation. In addition, NIH published a Request for Capability Statements in *FedBizOpps*, *NIH Guide for Grants and Contracts* (4/16), and the *Federal Register* (4/18) to ascertain whether current sanctuary entities with the requisite expertise and matching funds would be available to compete.

In May 2001, responses to the Request for Capability Statements were received. NIH determined that one or more submitting organizations appeared capable of fulfilling the Government's needs. In September 2001, NIH issued a Request for Proposals entitled, "Operation and Maintenance of a Sanctuary to Provide Lifetime Care for Chimpanzees." Chimpanzee sanctuary proposals were received in November 2001. In December 2001 NIH submitted the report to DHHS that Congress requested to address the number of chimpanzees and funding for care of chimpanzees.

During FY 2002, NIH will review chimpanzee sanctuary proposals and expects to award both the operation and maintenance contracts and a construction grant.

NCMHD PROJECT EXPORT CENTERS OF EXCELLENCE

Mr. Regula: What is the status of the development of comprehensive centers for health disparities?

Dr. Kirschstein: In February 2002, the National Center on Minority Health and Health Disparities (NCMHD) released three RFAs announcing the competition for its Project EXPORT Centers of Excellence Program. Each RFA provides a different funding mechanism through which eligible institutions can compete for funds. They are the R24, resource-related research project; the P20, exploratory planning grant and the P60, Center grant award. The purpose of using the three grant mechanisms is to encourage broad participation across institutions. Throughout the month of February and the beginning of March, NCMHD convened four technical assistance workshops to explain the RFAs and the application process to stakeholder institutions in four cities across the country. The meeting sites were: Dallas, TX; Morgantown, WV; Birmingham, AL and Seattle, WA. Letters of intent must be submitted by April 24. The application due date is May 24. These applications will be peer reviewed in July with awards being made in September.

CARIBBEAN PRIMATE CENTER

Mr. Regula: What is the status of the remediation of the inactive sewer at the Caribbean Primate Center?

Dr. Kirschstein: The remediation of the sewer system at the Caribbean Primate Center has been completed. The NIH Division of Engineering Services contracted the job to Jose Reig, an engineer, and the renovations were completed in May of 2001. The Director of the Caribbean Primate Center has conveyed to us that all of the old sewer components had been removed and replaced with a modern, upgraded sewage system. The people at the Caribbean Primate Center have been very pleased with the new system.

SELECT TRIAL

Mr. Regula: NIH is planning to conduct the largest-ever prevention study to determine if vitamin E and selenium can protect against prostate cancer. I understand this study is expected to take 12 years to complete. Tell us more about study.

Dr. Kirschstein: In July 2001 NCI and a network of researchers known as the Southwest Oncology Group (SWOG) launched the Selenium and Vitamin E Cancer Prevention Trial, or SELECT, to determine if these two dietary supplements can protect against prostate cancer, the most common form of cancer, after skin cancer, in men. NCI is receiving some supplemental support from the National Center for Complementary and Alternative Medicine for this trial.

The study will include a total of 32,400 healthy men age 55 and older. More than 400 sites in the United States, Puerto Rico, and Canada are recruiting participants for SELECT, which will take up to 12 years to complete. SELECT is the first study designed to look specifically at the effects of vitamin E and selenium, both separately and together, in preventing prostate cancer.

During this year alone, prostate cancer will be diagnosed in about 198,100 Americans and more than 31,500 men are expected to die of the disease. Risk factors for the disease include being over age 55, being black, or having a father or brother with prostate cancer.

Selenium and vitamin E, both naturally occurring nutrients, are antioxidants. They are capable of neutralizing toxins known as "free radicals" that might otherwise damage the genetic material of cells and possibly lead to cancer. These nutrients were chosen for study because of the results of two other large cancer prevention trials.

In a study of selenium to prevent nonmelanoma skin cancer in 1,000 men and women, reported in 1996, investigators found that while the supplement did not reduce skin cancer, it did decrease the incidence of prostate cancer in men by more than

60 percent. In another trial, published in 1998, in which beta carotene and vitamin E were tested to prevent lung cancer in 29,000 Finnish men who smoked, those who took vitamin E had 32 percent less prostate cancer.

COMPARISON OF THE PRESIDENT'S BUDGET AND APPROPRIATED FUNDS

Mr. Regula: Provide a table that shows the President's budget request for NIH, the projected number of competing research project grants, and the projected total number of research project grants for fiscal years 1998 through 2003 estimates. Provide a second table that shows for fiscal years 1998 through 2002 estimates, the NIH appropriation, the actual number of competing research project grants awarded, and the actual total number of research project grants.

Dr. Kirschstein: The information you requested is provided in the table below. Numbers of actual awards include projects funded through the Balanced Budget Act of 1997 and transfer from the Office of National Drug Control Policy (ONDCP).

NATIONAL INSTITUTES OF HEALTH
Comparison of President's Budget and Appropriations
(Dollars in Thousands)

	FY 1998 Actual	FY1999 Actual	FY 2000 Actual	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
President's Budget Request for Labor/HHS (total)	$13,078,203	$14,763,313	$15,932,786	$18,812,735	$23,041,902	$27,259,001
No. of Awards estimated						
Competing RPGs	7,112	8,267	7,617	7,641	9,158	9,854
Total	27,945	30,098	31,495	33,239	36,143	38,038
Appropriation for Labor/HHS	$13,647,843	$15,602,156	$17,793,587	$20,298,269	$23,175,843	
No. of Awards Actuals						
Competing RPGs	7,578	8,566	8,765	9,186	9,377*	
Total	28,399	30,223	32,184	34,286	36,633*	

* Estimated

NCMHD CONSTRUCTION GRANT FUNDING

Mr. Regula: How much is included in the request for the NCMHD construction grant program?

Dr. Kirschstein: A total of $8,180,000 has been provided in the President's fiscal year 2003 budget for the NCMHD Project EXPORT Centers of Excellence Program construction grants.

NIH SECURITY IMPROVEMENTS

Mr. Regula: Provide a breakout of the $80 million requested for improvements to the physical security of the NIH campus.

Dr. Kirschstein: The proposed improvements are the second and largest increment of the physical security plan that NIH is implementing as part of a comprehensive security program aimed at providing a safe and secure environment for the conduct of its mission. The plan follows a system of concentric levels of security from the outermost areas of the site and works inward, toward individual buildings and areas within buildings. The first element of the security plan, a perimeter fence around the Bethesda campus, is being provided through FY 2002 funding. The FY 2003 request for $80 million completes the perimeter security system, provides necessary infrastructure upgrades and addresses sensitive building areas.

The request comprises the following projects:

- a Visitor Center for welcoming and screening visitors and vehicles, issuing visitor passes and providing central campus-wide transportation services;
- a Delivery Clearance Center for managing and screening deliveries of scientific and other equipment and materials to the campus;
- an internal Campus Loop Road for effective emergency response and efficient circulation of a large number of commercial and employee vehicles;
- enhancements to the information technology infrastructure to increase capacity of communications systems, minimize network security breaches and provide backup capabilities;
- enhancements to specific laboratories and facilities to make building envelopes more resistant to the effects of hostile actions and upgrade electronic building security systems; and
- a similar range of security projects at a smaller scale for the Rocky Mountain Laboratory, an NIH facility of the National Institute of Allergy and Infectious Diseases at Hamilton, Montana.

These improvements are consistent with direction given by the Executive Branch (Department of Justice, Office of Homeland Security, et.al.) and the Department of Health and Human Services (HHS), "best practices," as well as the HHS Inspector General. Together, other enhanced technology systems and operational changes that NIH is implementing and these planned projects will bolster our ability to prevent, detect and respond to a variety of security risks, and will enable NIH address effectively a range of federal "alerts levels" as necessary.

DEPARTMENTAL INFORMATION TECHNOLOGY INITIATIVE

Mr. Regula: How much is included in the request to support the Department's information technology initiative?

Dr. Kirschstein: NIH will provide approximately $27.28 million for Departmental information technology (IT) initiatives as follows:

Program Support Center HHS - $6.10 million

Unified Financial Management System - $ 0.57 million

HHS IT Infrastructure - $20.61 million

ONDCP

Mr. Regula: You will receive $9.5 million from ONDCP this year. How will you use this funding?

Dr. Kirschstein: Under the Memorandum of Understanding between the National Institute on Drug Abuse and ONDCP, $7 million of the $9.5 million will go to Westat and its subcontractor, the Annenberg School for Communications at the University of Pennsylvania, to cover the costs of the final year of the evaluation of the National Youth Anti-Drug Media Campaign. Spearheaded by the Office of National Drug Control Policy (ONDCP), the Campaign is a concerted effort by both the public and private sectors to reduce drug use in the United States. It is based on principles and objectives that have been derived from decades of scientific research. Because of NIDA's scientific expertise, ONDCP asked NIDA to manage the contract to evaluate the outcomes and impact of the Campaign on parents and their children concerning attitudes, knowledge and behaviors with regard to illegal drug use among youths and to measure the Campaign's impact at the community level. This request was in response to legislation which requested ONDCP to establish "a system to measure outcomes of success of the national media campaign."

The remaining $2.5 is under review.

PAYMENTS TO GSA

Mr. Regula: Why do you anticipate payments to GSA to increase 24 percent in fiscal year 2003?

Dr. Kirschstein: The major factor contributing to this increase is a 27 percent anticipated increase in GSA rent payments by the NIAID, which estimates its GSA rent payments will increase $2 million for the space in Rockville, MD to house additional manpower to implement the FY 2003 counter-bioterrorism program.

INCREASE IN TRAVEL FUNDING

Mr. Regula: Why do you anticipate a 13.5 percent increase in your travel budget?

Dr. Kirschstein: The NIH plans to use a large portion of the travel increase (45%) to support the increase for counter-bioterrorism initiatives. Such activities will include: Attending meetings with regard to collaborative research projects that focus on counter-bioterrorism agents; Overseeing clinical trial efforts relating to counter-bioterrorism agents; Conducting site visits for several new regional and specialized centers in the U.S.; Conducting visits to ensure compliance with federal guidelines with regard to reagent respositories and specialized animal holding facilities for extramural investigators; Meeting with representatives from industry, academia and other federal agencies to provide guidance, advocate initiatives, advocate scientific positions, gain insight and exchange information on matters relating to counter-bioterrorism. In addition NIH plans to support significant expansion in overseas research, particularly related to HIV/AIDS including support of a phase III trial in Thailand in Fiscal Year 03 and other clinical trials in several countries in Africa and Southeast Asia.

The rest of the increase will be used to support travel expenses integral to the mission of NIH such as: bringing patients to Bethesda to participate in intramural clinical trials that furthers the translation of basic laboratory research into clinical applications; conducting pre- and post-award reviews to allow the proper scientific and administrative management of appropriated funds entrusted to NIH for grants and contracts; meetings of advisory boards and councils to provide the essential second level of peer review mandated before the award of grants and contracts as well as providing guidance on program direction; attending scientific meetings, conferences and symposia to allow research results to be disseminated quickly, lessening the time between achievement and publication, as well as providing a medium for young researchers to establish scientific credentials and helping the recruitment of new researchers to NIH.

NIH SUCCESS RATES

Mr. Regula: Why haven't we seen an increase in the NIH success rate over the past five years?

Dr. Kirschstein: The dramatic budget increases NIH has seen over the last five years has resulted in greatly increased opportunities for researchers, as demonstrated by an increase in the number of competing awards during the five year span closing in FY 2003 by a projected 30%. In return, the research community has been invigorated, clearly demonstrating its dynamic nature and a 38% increase in applications submitted in areas worthy of biomedical investigation during this same five year span. Science is alive and well, and it is precisely because of this that success rates have remained relatively constant as we have seen the breadth and width of quality applications increase.

NIBIB SUCCESS RATE

Mr. Regula: Why is the NIBIB success rate projected to decrease from 31 percent in fiscal year 2002 to 14 percent in fiscal year 2003?

Dr. Kirschstein: The National Institute of Biomedical Imaging and Bioengineering (NIBIB) has put forward a vigorous agenda for research in its first year, and has met with the scientific community across the country to stimulate interest in new research areas that have been identified and that are within the mission of the Institute. We anticipate that these steps will result in a rapid rise in the number of research grant applications received by NIBIB in the next year, reflecting the high degree of enthusiasm within the research community.

There are several factors that affect NIBIB's ability to estimate future success rates. They include the size of the commitment base, the increase in average costs, and the use of funds for co-funding projects with other ICs. In the absence of any history of applications received, it is difficult to predict with certainty the number of applications that NIBIB will receive in FY 2002 and FY 2003. The high level of enthusiasm demonstrated by the research community, however, is expected to continue.

SUCCESS RATES

Mr. Regula: Why is the NIEHS success rate projected to decrease from 27 percent in fiscal year 2002 to 21 percent in fiscal year 2003?

Dr. Kirschstein: In order to take advantage of new technologies and approaches to fund important initiatives such as toxicogenomics research, asthma research, the Sister Study, clinical research, and Parkinson's disease research, the NIEHS is using a variety of mechanisms other than single project R01 grants. Many of these initiatives, instead are being funded through the R&D contracts mechanism. While this results in a short-term decline in the success rate, NIEHS believes that the impact of these new programs will be substantial and in some cases provide information that will be crucial for future investigator-initiated, hypothesis-driven research projects.

INCREASED FUNDING IN RESEARCH AND DEVELOPMENT CONTRACTS

Mr. Regula: Research and development contracts have increased from $793 million in fiscal year 1998 to an estimated $2.6 billion in fiscal year 2003. The majority of this increase occurs in fiscal years 2002 and 2003. Explain the reason for this in further detail.

Dr. Kirschstein: The NIH awards research and development (R&D) contracts to non-profit and commercial organizations for scientific inquiry directed toward particular areas of research and development. Their purpose is to utilize advances in knowledge and technology to search for solutions to specific questions. R&D contracts are also

used to acquire research-related services. For example, clearinghouses which provide disease-related information to the public, such as the Alzheimer's Disease Education and Referral clearinghouse or the National Digestive Diseases and Diabetes Information clearinghouses, are supported by R&D contracts. Contracts are used for patient recruitments into clinical trials, and for vaccine development efforts, in HIV, for example.

Research and development contracts increase by close to 30 percent in FY 2002, and then by nearly 45 percent in FY 2003. These larger increases in R&D contracts, as compared to other extramural mechanisms, are driven by several factors.

The FY 2002 increase includes $28 million to support the two new loan repayment programs (LRPs)–the Extramural Clinical Research LRP, and the Extramural Pediatric Research LRP. Each individual who will participate in these programs signs a contractual agreement with NIH regarding loan repayment by the government. The FY 2003 President's budget request nearly doubles these contract programs by providing $25 million over the FY 2002 estimate.

The threat of bioterrorism became a reality in the United States with the intentional delivery of anthrax spores through the mail through print media, television and government offices. A large portion of the increased bioterrorism activities will be supported through R&D contracts. Included as part of the R&D contracts increase within NIAID in FY 2003 is an additional $225 million over the FY 2002 amount of $43 million to support the Administration's initiative to develop biomedical research tools to detect, diagnose, prevent and treat infections by biological agents that could serve as possible weapons. The FY 2003 President's budget request also includes an additional $250 million for anticipated procurement of anthrax vaccines currently under development and testing.

In the FY 2003 President's budget request, a total of $49 million is directed toward collaborative research projects with the Department of Defense, including development of an HIV/AIDS vaccine, research into the use of free electron lasers for surgical debridement, and research into radiation treatment.

The FY 2003 President's budget request will allow NIH to continue its FY 2002 support of $100 million for the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis, to further the NIH's efforts to prevent and alleviate these diseases. The full $100 million would be funded through R&D contracts in FY 2003.

Funding for AIDS vaccine research through R&D contracts would increase by $22 million in the FY 2003 President's budget request, bringing the total to $63 million.

NIH is mandated to support small businesses conducting research and development projects that may lead to commercial products or services. A set-aside of 2.5% for the Small Business and Innovation Research program (SBIR) and 0.15% for

the Small Business Technology Transfer Research (STTR) program determines the minimum funding level. This program is funded by R&D contracts as well as grants, and $2 million of the increase in R&D contracts is accounted for by this set-aside.

CHEMOPREVENTION

Mr. Regula: Describe the concept of chemoprevention in further detail.

Dr. Kirschstein: Years of scientific research have demonstrated that the diseases of cancer occur not as single, catastrophic events, but rather as the result of a complex and long-evolving process. The process of carcinogenesis can take decades to complete, providing time and opportunity to intervene to stop, reverse, or delay its progress before the clinical appearance of advanced or invasive cancer.

Chemoprevention is the science of intervening to stop the cancer process using pharmacologic, nutritional, or hormonal/endocrinologic agents. Chemoprevention studies and clinical trials focus on learning whether certain medicines (pharmacologics and hormonal agents), vitamins, minerals, or food supplements (nutritional agents) can prevent, reverse, or delay cancer. In addition to determining if the agents can prevent cancer, it is of paramount importance that the safety and full effects of the agents be understood. In order for a prevention agent to be useful it must both prevent the cancer and not cause effects that may harm the person's health.

Chemoprevention trials are designed to help people who have not previously had cancer, but who may be at-risk due to hereditary and environmental factors or who have precursor lesions of cancer. Chemoprevention trials are also designed to prevent a second or new type of cancer from developing in people who have had cancer.

One of NCI's most successful chemoprevention trials was the Breast Cancer Prevention Trial, which showed that Tamoxifen reduces breast cancer incidence by 49 percent in women at increased risk of the disease. The trial tracked 13,000 women and also showed that tamoxifen works like estrogen to preserve bone strength, decreasing fractures of the hip, wrist, and spine in the women who took the drug. In October 1998, the FDA approved the use of tamoxifen to reduce the incidence of breast cancer in women at increased risk of the disease. Tamoxifen has been approved by the FDA for more than 20 years to treat women with breast cancer and has been in clinical trials for about 30 years.

The results from the Multiple Outcomes of Raloxifene Evaluation, or MORE trial, showed that the osteoporosis prevention drug raloxifene (Evista®) reduced the incidence of breast cancer in postmenopausal women with osteoporosis. Raloxifene was approved in December 1997 by the FDA to prevent osteoporosis.

The current Study of Tamoxifen and Raloxifene or STAR is a breast cancer prevention clinical trial designed to determine whether the osteoporosis prevention and treatment drug raloxifene (Evista) is as effective as tamoxifen (Nolvadex) in reducing breast cancer risk. STAR is a study of the National Surgical Adjuvant Breast and Bowel Project (NSABP) and is supported by the NCI. The trial began enrolling participants in July 1999. The NSABP has undertaken several novel strategies to encourage minority women to participate in STAR, which include the STAR Community Outreach Program for Education (SCOPE) underway in ten cities in the United States. The goal of SCOPE is to educate minority women about breast cancer, which may ultimately lead to their more widespread participation in clinical trials. Moreover, STAR is supported by the National Medical Association (NMA), a network of more than 20,000 African-American physicians. As a first effort, the NSABP is working closely with Region II of the NMA, which includes members in Pennsylvania, Delaware, Maryland, Virginia, West Virginia, and the District of Columbia, to pilot a unique outreach project. The initial participation is in Philadelphia with plans to extend outreach into the rest of Region II and eventually throughout the NMA organization. Recent analyses of the use of tamoxifen in women with breast cancer show that tamoxifen works equally well in white and African-American women.

NONCOMPETING RESEARCH PROJECT GRANTS IN FY 2004

Mr. Regula: For each Institute and Center, provide the level of funding it would take to maintain its commitment base in fiscal year 2004.

Dr. Kirschstein: At this time NIH models for FY 2004 and beyond are aggregate in nature. We presume a higher level of accuracy in aggregate models at this juncture than we could hope to achieve for each Institute and Center by modeling centrally using a standard set of assumptions. If NIH is provided with the 2.1% inflationary increase in FY 2004 as laid out in this request, we foresee paying all noncompeting grants at committed levels.

COMPETING RESEARCH PROJECT GRANTS IN FY 2004

Mr. Regula: Provide a table that shows, for each Institute and Center, the number of new and competing grants that could be funded in fiscal year 2004 if NIH were provided level funding at the fiscal year 2003 President's request and at the President's proposed fiscal year 2004 budget increase.

Dr. Kirschstein: At this time NIH models for FY 2004 and beyond are aggregate in nature. We presume a higher level of accuracy in aggregate models at this juncture than we could hope to achieve for each Institute and Center by modeling centrally using a standard set of assumptions - which likely wouldn't hold for every IC in actuality. If NIH is provided the levels in the President's request for FY 2003 and FY 2004 respectively, we foresee having approximately the same number of competing aggregate grants in FY 2004 as in FY 2003.

KNOWLEDGE FROM BIOMEDICAL RESEARCH

Mr. Regula: With the doubling effort of the past five years, we are starting to experience an explosion of knowledge that is leading to new treatment and prevention protocols. Are we creating a bottleneck of discoveries with limited ways to put them to use?

Dr. Kirschstein: Successful outcomes from the research program mean a continuing flow of high quality research – discoveries of new fundamental knowledge, applications of new therapies, diagnostics, prevention, and development of new research tools – from extramural grantees and the intramural laboratories. It also means timely dissemination of scientific results and research-based health information and expeditious transfer of the results of its medical research to the broader research community, both public and private, for use in further research and development.

NIH develops and disseminates informational materials to individuals and groups, including medical and scientific organizations, industry, the media, and volunteer and patient organizations. Information dissemination efforts have expedited the translation of NIH's scientific advances and technologies into important diagnostic, preventive, and therapeutic products. NIH disseminates information on scientific findings and technologies to scientific and other health professionals through various avenues: scientific publications, workshops and symposia, scientific meetings, consensus development conferences, press releases, special physician education programs, and clinical alerts concerning immediate health and safety issues. NIH also provides access to information about scientific articles, NIH research grants, clinical trials and treatment through extensive electronic databases.

Additionally, as a federal R&D agency, the NIH has a statutory mandate to engage in technology transfer activities for discoveries that must be brought to the market by a company in order to benefit the public. The requirement is applied to recipients of NIH research grants and contracts as well as our own intramural research activities. In return for title to inventions developed under NIH support, recipient institutions enter into agreements (licenses) with commercial partners to undertake additional research and development with the invention and ultimately bring a product to market. Internally, we evaluate new research discoveries, seek patent protection if further development is needed, and market the technology to potential licensees. These companies are monitored in their efforts to move the technology to the market place in an expeditious manner.

The NIH collaborates with other Federal agencies and Departments as well as the private sector to further the NIH mission and facilitate the flow of new biomedical knowledge to the private sector for development and commercialization. These collaborative efforts help to generate new opportunities to put to use new knowledge about biological systems and strategies for the diagnosis, treatment, and prevention of disease and disability.

IMPLEMENTATION OF STEM CELL RESEARCH POLICY

Mr. Regula: Are you satisfied with the progress of implementation of the President's stem cell research policy?

Dr. Kirschstein: The answer is still under review.

NIH-IDeA

Mr. Istook: Please outline the current status of the NIH-IDeA program to assist underrepresented states in receiving NIH grants.

Dr. Kirschstein: The NIH IDeA program staff have developed two programs, the Centers of Biomedical Research Excellence (COBRE) and the Biomedical Research Infrastructure Network (BRIN). The two are intended to enhance institutional research infrastructure at the institutions--the three major components include 1) the recruitment of established investigators to mentor junior faculty along with graduate and post-graduate students so as to increase the pool of trained investigators, 2) the provision of funds to upgrade laboratory facilities and core research technologies, and 3) the provision of modern resources, including instrumentation to research laboratories. The BRIN program supports the development of state-wide networks among eligible institutions and encourages sharing of research resources among participating network institutions. The BRIN includes institutions ranging from the community college to those giving doctoral degrees.

To date, 29 COBRE awards and 24 BRIN awards have been made to the 23 eligible states and Puerto Rico. In FY 2002, states may submit competitive supplements to request funds to expand their BRINs, compete for new COBREs and also submit applications to upgrade their facilities and purchase research instrumentation. Approximately $55 million is available for those new awards. Ongoing support for previously awarded grants is approximately $105 million.

METALS IN MEDICINE

Mr. Istook: The Metals in Medicine Initiative has been started by NIH. Please give a report outlining the progress to date.

a) How many grants have been issued under this initiative?

b) How many grants have been issued on Chromium and Diabetes Nutrition?

c) How many grants have been issued on Mercury?

i) How many have dealt with Mercury metabolism and brain function?

ii) How many have dealt with diagnosing the mercury load in the brain?

iii) Have any grants been issued to answer the key question CDC is looking at, what is it in the brain's metabolism that requires it to seek mercury in the compound that it bonds Mercury into? Is the brain seeking a different element and settling for Mercury?

d) How many grants have been issued on lead?

e) How many grants have been issued on the known metals in nutrition?

i) Zinc

ii) Copper

iii) Selenium

iv) Molybdenum

v) Please list others

Dr. Kirschstein: The "Metals in Medicine" program announcement (PA01-071) was issued on March 19, 2001. Thus far, 35 proposals have been received; two will be funded as a result of the January Council review; two are pending Council review in May; and six are still to be subjected to the first level of peer review.

The use of chromium supplements among individuals with diabetes is not an uncommon practice. Evidence from small, non-controlled clinical trials suggests that chromium supplementation may alleviate symptoms associated with diabetes and reduce the need for extraneous insulin in patients with type 2 diabetes. The results of a systematic review together with the findings of an Office of Dietary Supplements (ODS) scientific workshop provided convincing reasons to support small-scale, focused clinical studies and to encourage basic research into how chromium affects insulin secretion.

In July 2001, as follow-up to the chromium and diabetes workshop, the ODS, the National Center for Complementary and Alternative Medicine, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) co-sponsored a Program Announcement entitled "Chromium As Adjuvant Therapy for Type 2 Diabetes and Impaired Glucose Tolerance" (PA-01-114). "The purpose of the PA announcement was to encourage (1) basic studies of chromium action on insulin secretory and signaling pathways and (2) clinical studies to assess the safety and efficacy of chromium as an adjuvant treatment of type 2 diabetes and/or impaired glucose tolerance."

The NIDDK is currently supporting two grants, both awarded to the same investigator, directed at evaluating the potential benefits of chromium in type 2 diabetes. One grant, entitled "Chromium and Insulin Action," provides support for collection of preliminary data, including evaluation of possible toxicity, which may be useful in designing a future clinical trial. A second grant is based at a General Clinical Research Center supported by the National Center for Research Resources, and is entitled "Effect of Chromium Picolinate on Glucose Control in Type 2 Diabetic Patients." The NIH is hopeful that the ongoing Program Announcement will encourage additional grant applications for potential funding by the three participating NIH components. As with other NIH research solicitations, the extent of funding under this Program Announcement will depend on the number and scientific merit of the applications that are received. The Program Announcement is active for three years.

NIEHS has not received any grant applications specifically in response to the Metals in Medicine Initiative, PA01-071 on mercury. However, the NIEHS has primary assignment on a broad array of research to identify the effects of mercury compounds on brain function and to understand the biological basis for these effects. Currently there are 28 research projects that focus on mercury. Seven of these are specific to effects of mercury on the brain. NIEHS supports research projects which range from clinical studies of the effects of prenatal mercury exposure on cognitive performance in children to studies that aim to understand how mercury compounds enter the brain and why some cell types and brain regions are more susceptible to mercury toxicity.

Although NIEHS has not received grant applications through the Metals in Medicine initiative, NIEHS has primary assignment for seven research projects that are studying the mechanism of mercury toxicity in the brain, in both (1) animal models and (2) clinical studies that study the effects of methyl mercury exposure on neurobehavior and neurofunction in children.

Currently there are no grants dealing with diagnosing the mercury load in the brain.

Although NIEHS has not received grant applications through the Metals in Medicine initiative, NIEHS has primary assignment for one grant that is specifically related to studies focused on mercury transport across brain cell membranes.

In response to PA01-071, one new grant on lead will likely be issued after the May Council. In response to PA01-071, one new project will look at zinc and two will look at iron. For a more general answer, please see the Table 1 below.

TABLE 1. NUMBER OF NIGMS and NIH AWARDS IN FY2001
All Mechanisms with Primary, Secondary, or Tertiary Emphasis on the indicated metal.

Metal	NIGMS	NIH
Mercury	5	37
Lead	3	70
Cadmium	7	42
Zinc	45	131
Copper	45	104
Selenium	2	61
Molybdenum	17	23
Vanadium	9	17
Chromium	1	21
Manganese	30	66
Iron	126	318
Cobalt	16	32
Nickel	10	25

Source IMPACII QVR System, Queried using CRISP Term Search, All Keywords.

HYPERBARIC OXYGEN INITIATIVE

Mr. Istook:

a) Since the Hyperbaric Oxygen Initiative began two years ago, how many grants have been awarded regarding research in Hyperbaric Oxygen.

b) Please outline for the Committee the progress of this initiative and how many of the Institutes and Centers are involved in this project?

c) Identify each of the Institutes and Centers and the primary person who has been assigned to examine this therapy within the overall research portfolio.

Dr. Kirschstein: Over the past several years, NIH has supported a number of studies of hyperbaric oxygen therapy (HBOT) in a wide range of disease applications. Some areas of focus have included: the effects of HBOT on radiation-induced blood vessel damage, recovery from laryngectomy, and repair after stroke-related brain injury. Some of this research is being conducted under a large center grant designed to examine the mechanisms of action, safety, and clinical efficacy of HBOT. NIH has also awarded a grant to the Undersea and Hyperbaric Medical Society to organize their scientific information resources on hyperbaric medicine and make them more widely available.

Due to the number of potential indications for HBOT, many NIH Institutes and Centers (ICs) have supported work in this area, including the National Center for Complementary and Alternative Medicine and the National Institute of Neurological Disorders and Stroke, among others. NIH welcomes new applications for study of HBOT for any medical indication, and is eager to fund well-designed preclinical and clinical studies. To move this research forward, NIH staff have met with investigators in the field and have encouraged them to apply for funding.

Assignment of a grant to a specific Institute or Center (IC) depends upon the biological system or clinical indication being evaluated. Thus, many ICs could potentially support HBOT research in the future. Staff contacts are available in every IC, depending upon the nature of the study (basic science or clinical) and the specific research questions being addressed (e.g., repair after brain injury). Program staff at most ICs are typically responsible for specific scientific or disease areas that are appropriate to their expertise, and are not usually assigned responsibility for a specific intervention that might be used for a broad range of disorders. Investigators interested in applying for NIH funding are urged to contact the division of extramural research in the IC that is most closely aligned with the indication they are exploring, for further assistance.

BAYH-DOLE ACT

Mrs. Northup: Given the dramatic increases in federal funding for the National Institutes of Health over the last several years, I am tremendously concerned with situations involving federal support of medical research, the patents of which are then controlled by a private-for-profit company so that no other non-profit research can build upon the patented material. What are your plans to ensure that other researchers are not stalled in clinical trials, clinical trials that are critical to solving a host of diseases, because of licensing issues over research that resulted from federal dollars and that researcher's own work?

Dr. Kirschstein: For sometime the NIH has been concerned with the sharing of findings and materials developed with federal funds. In 1999, the NIH issued a document entitled "Sharing of Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts." The document states that institutions licensing a patented invention or unpatented materials for commercial purposes should retain rights to permit all other entities to use the invention for research purposes. This type of license structure keeps the research enterprise robust by preserving the right of researchers to use the technology.

The sharing document is now included as a term and condition for NIH grants and contracts. Additionally, the Technology Transfer Commercialization Act of 2000 amended the Bayh Dole Act to state that the objective of the act was to bring about commercialization "without impeding future research and discovery." This additional language was added by the US Senate to support the NIH policy on sharing of biomedical research resources.

The NIH is continuing to work with recipient institutions and companies providing materials to NIH researchers to ensure they understand the requirements of the NIH policy and implement it appropriately. We believe this policy and the NIH actions are having a positive effect on the flow of research by permitting researchers to access materials they may not have been able to access previously. We understand that this is a long term effort, but we are committed to the objectives of the policy.

POST DOUBLING OF THE NIH BUDGET

Mrs. Northup: After the final year of our plan to double the funding for NIH over five years, how will you manage your research portfolio when the agency goes back to receiving much smaller increases, perhaps only inflationary costs?

Dr. Kirschstein: The FY 2003 Budget request for National Institutes of Health (NIH) totals $27.3 billion, a $4 billion increase over last year's funding level. The Administration is carefully considering future funding options to ensure that this valuable research is not compromised, but can be advanced. Strategies to deal with smaller budget increases in FY 2004 and beyond were incorporated into the FY 2003

President's Budget. Budget plans benefit from these costs because of the absence of financial commitment in future years. This strategy enables the NIH to maintain commitments for non-competing grants and to continue supporting approximately the same number of new and competing research project grants in FY 2004. Should one-time costs in FY 2003 be directed to high priority or emerging areas as was the case with bioterrorism last year, there could be significant effect on the NIH grant portfolio. The Administration is committed to ensuring that NIH remains the world's leading biomedical research institution.

PREPARING RESEARCH COMMUNITY FOR FUTURE NIH BUDGET

Mrs. Northup: What are you doing to prepare the research community for smaller budget increases?

Dr. Kirschstein: The FY 2003 Budget request for National Institutes of Health (NIH) totals $27.3 billion, a $4 billion increase over last year's funding level. This unprecedented increase fulfills President Bush's commitment to double the NIH budget in five years from the FY 1998 appropriation level. The Administration is carefully considering future funding options to ensure that this valuable research is not compromised, and can be advanced. Among a host of issues, the Administration will be considering policies that give NIH financial flexibility in awarding grants and funding options that consider NIH's budget in the context of other science funding. NIH anticipates that at the FY 2004 level in the FY 2003 Request, it will be able to fund approximately the same number of competing research project grants as in FY 2003. The Administration is committed to ensuring that NIH remains the world's leading biomedical research institution.

We have reinforced to the research community the important principle that NIH supports the best science through peer review. The one constant factor in changing budget situations has been the NIH peer review system. It is the cornerstone of the scientific enterprise and it assures researchers, and the public, that the most competitive, highly meritorious projects will be funded. The scientific community understands that there are many pressures on the federal budget and I hope that they understand that we will look very carefully at how we can work within the budget framework and yet support the overall scientific enterprise.

INFORMING THE PUBLIC

Mrs. Northup: What are you doing to prepare the disease-advocacy community?

Dr. Kirschstein: The NIH Office of the Director and the various Institutes and Centers, primarily through their public liaison offices, keep in constant touch with patient advocacy groups, professional associations, and others interested in the work of the NIH. We update these groups frequently about the NIH budget and about our

programs and activities. At the upcoming meeting of the NIH Council of Public Representatives (COPR), the NIH Acting Director will present an overview of the President's budget proposal for fiscal year 2003, as well as a report on the hearings of the Senate and House appropriations hearings on the NIH budget.

CANCER IN THE MEDICALLY UNDERSERVED

Mr. Cunningham: Medically underserved communities suffer disproportionately high cancer rates and other health challenges. How are NIH and the National Cancer Institute (NCI) responding to this problem? Should there be a push by NCI to help study and reduce high cancer rates in medically underserved communities?

Dr. Kirschstein: The NCI for many years has been addressing questions related to the medically underserved and the cancer health disparities that occur in these communities. The Institute continues to expand support for research aimed at eliminating these disparities. The activities of the NCI directed to this effort are an integral part of the research agendas of all the Institute's divisions and offices. To direct the implementation of the NCI Strategic Plan to Reduce and Ultimately Eliminate Cancer Health Disparities and to provide an organizational locus for the Institute to bridge the gap between research discoveries and cancer care delivery, NCI has created the Center to Reduce Cancer Health Disparities (CRCHD), and is honored to have recruited Dr. Harold P. Freeman, as Director of the Center. Dr. Freeman is internationally recognized for his unprecedented contributions to and tireless advocacy for cancer in the poor and medically underserved. His expertise and leadership will enable the Institute to substantially strengthen and sustain effective efforts to achieve reductions in cancer incidence and mortality in medically underserved communities.

NCI is moving forward to address the problem of cancer in the medically underserved. In FY 2001, the NCI supported approximately $140 million to address this unequal burden of cancer in medically underserved communities. In its five-year strategic plan, the Institute outlines plans to double its support to address this issue.

In FY 2002 the Institute identified this issue as a major challenge for NCI in its annual plan and budget proposal. The Institute's commitment to this challenge was marked by the creation of the NCI Center to Reduce Cancer Health Disparities in December 2000. Through the Center's leadership, NCI continues to expand the number and breadth of initiatives to address this challenge to science as well as moral and ethical dilemma for our Nation. NCI-supported research has helped us make enormous strides in understanding how biological and behavioral factors determine risks for developing or dying from cancer and how interventions can modify there risks. Little is known about the effects of social position, economic status, cultural beliefs and practices, and environmental exposures on cancer risk. As a result, NCI is working in several high priority areas to better understand the relationship about what we know about cancer care and how and to whom it is provided. Highlights of recent research to address cancer health disparities include:

- Treatment Disparities for Lung Cancer Related To Surgical Practices - An NCI-funded study found that the lower survival rate among African American patients with early-stage, non-small-cell lung cancer, as compared with White

patients, is largely explained by the lower rate of treatment through surgery among African Americans. The rate of surgery was 12.7 percentage points lower for African American patients than for White patients (64.0 percent versus 76.7 percent). For patients who had surgery, survival was similar for the two racial groups. NCI is examining the issues emerging from a growing number of similar peer-reviewed studies published in leading medical journals showing that black patients, when compared with white patients of similar socio-economic status, insurance coverage, health status, and diagnosis, tend not to receive the same treatments as white patients. A limited number of studies have also shown that other race, and ethnic minorities, and underserved populations experience similar outcomes. The unsettling nature of the conclusions drawn from this and other similar studies prompted NCI's Center to identify this issue as a major focus of analysis in its first full year of operation. In January 2002, NCI convened a group of experts in a number of relevant fields to begin to examine the complex components of the problem and to begin to develop effective interventions to eliminate disparities in cancer care treatment.

- Unnecessarily High Cervical Cancer Mortality Must Be Addressed - NCI is examining the problems associated with why, despite a three-fold reduction in cervical mortality nationwide in the past 50 years, counties stretching from Maine southwest through Appalachia to the Texas/Mexico border as well as in many Southeastern states and in the Central Valley of California have experienced persistently higher cervical cancer mortality rates. To address this 50-year disparity for a cancer from which no woman in this Nation should die, NCI and its national, state, and local partners are working to: synthesize research knowledge; identify core findings; articulate program and policy options; and, disseminate this information to Federal, state, and local decision makers.

- Cancer Survivorship in Minority and Underserved Addressed by Cancer Centers - Investigators at NCI-supported Comprehensive Cancer Centers are using supplemental funding to examine: the physical and psychosocial needs of medically underserved cancer survivors and/or their families and how these needs compare with those found in cancer survivors and/or their families from majority populations; sociocultural variables that affect cancer survivorship, particularly those that affect quality of life; the nature and effectiveness of existing post-treatment medical and support services designed for cancer patients from underserved communities; the effectiveness and feasibility of behavioral measures and interventions aimed at assessing and reducing secondary physical and psychological consequences for minority or underserved cancer survivors and their families.

NIH FUNDING FOR DIABETES RESEARCH

Mr. Cunningham: There has been much publicity recently regarding the rapid rise in diabetes prevalence. In fact, both CDC and Secretary Thompson have identified diabetes as an "epidemic." Can you explain why even in light of this drastic increase in diabetes, the percentage of the NIH budget devoted to diabetes since 1987 has decreased dramatically?

Dr. Kirschstein: While it is true that funding for diabetes research NIH-wide as a percentage of the NIH budget declined from 3.9 percent in fiscal year (FY) 1987 to a low of, 2.5 percent in FY 1997, it has been on the rise since then. For fiscal year 2002, we estimate that 3.4 percent of the NIH budget will be devoted to diabetes research. This represents a 36 percent increase in the proportion of the NIH budget directed toward diabetes since 1997. However, during this same time period, the percentage increase of NIH funding for diabetes research will significantly outpace the percentage increase in the overall NIH budget: the diabetes research budget will increase by 144 percent, from $320 million in 1997 to an estimated $781 million in 2002, while the NIH budget will have increased 82 percent over this same time period, from $12.77 billion to an estimated $23.28 billion.

The diabetes-specific dollar increase has been aided by the special funds for type 1 diabetes research that were first appropriated in FY 1998. The NIH portion of these funds was $27 million per year from FY 1998 through FY 2000. That amount was increased to approximately $97 million per year in FY 2001 as a result of additional congressional action. This funding, which is authorized and appropriated through FY 2003, has permitted the NIH to pursue many scientifically promising initiatives in diabetes research.

NIH FUNDING FOR DIABETES RESEARCH

Mr. Cunningham: Recently, both CDC and Secretary Thompson have called diabetes an "epidemic." All data indicates that the rapid rise is not slowing down. However, the rise in diabetes prevalence has not been matched by a similar drastic increase in diabetes research spending. Given the recent history of equal across-the-board percentage increases at NIH Institutes, what mechanisms do you have in place to respond to epidemics such as diabetes? Why have these mechanisms not ensured that diabetes research spending increased at an appropriate rate? What can you do now to ensure that the research funding response to this diabetes epidemic is indeed appropriate?

Dr. Kirschstein: The amount of funding for diabetes research NIH-wide has increased every year since at least 1976, with the most dramatic dollar increases coming since 1997. For fiscal year (FY) 2002, we estimate that the NIH will invest about $781 million in diabetes research, representing an increase of about $93 million over FY 2001. The increases in the NIH budget since 1997 have allowed the NIH to

undertake many new and promising initiatives in diabetes research. There are mechanisms in place within the NIH to ensure that our diabetes research effort is well-mobilized and highly coordinated among our institutes and centers, as well as with other federal agencies. These include the Diabetes Mellitus Interagency Coordinating Committee (DMICC). The size and scope of the NIH-wide diabetes research portfolio reflect the scientific synergism of this Committee, as well as the scientific advice and recommendations of external diabetes experts and organizations. With diabetes reaching epidemic proportions, diabetes research is accorded very high priority within the NIH. We will continue to invest substantial resources in this area, within the context of our budget and our obligation to appropriately support other programs within the NIH mission.

Ultimately, resource allocation to disease- and non-disease-specific programs alike is based on available funds, the competition for those funds, and the funding of grant applications that are judged to be highly meritorious within the NIH peer review system. Most awards for research are made to investigators who apply for grants to pursue research fields and scientific concepts that they have developed independent of NIH research solicitations or stated research interests. While the NIH stimulates this type of "investigator-initiated" research to a certain degree through the sponsorship of workshops and conferences, the NIH has minimal control over this source of applications because investigators are free to propose research in any area of their choice. Historically, this mechanism of funding grants has proven extraordinarily successful in enabling major scientific discoveries, as well as the incremental, but vital, accumulation of new knowledge in basic biology and medicine.

To complement the investigator-initiated research mechanism, all of the NIH institutes and centers use a certain amount of funds to encourage research in areas in which there are particular scientific opportunities, unmet scientific needs, public health issues, congressional directives, or other special emphases. Using this mechanism, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has coordinated and implemented a host of basic and clinical initiatives to address the growing problem of diabetes. These initiatives resulted in large part from the efforts of the DMICC and from close, ongoing consultation with non-federal experts and advisory groups. The NIH diabetes research effort, led by the NIDDK, will continue to develop and implement new and expanded program initiatives, again, within the context of our available budgetary resources and responsibilities to our overarching research mission.

Again, Mr. Cunningham, I can only say that diabetes research is a very high priority with the NIH, that we have mechanisms in place to catalyze this research across the many institutes and centers of the NIH, and that we will invest funds strategically and in a broad consultative way to ensure that major scientific needs and opportunities in diabetes research are addressed.

DIABETES RESEARCH WORKING GROUP REPORT

Mr. Cunningham: Looking over the report issued by the Diabetes Research Working Group, it is clear that we still are well short of their budget recommendations for diabetes research. As Acting Director of NIH, what are you doing to ensure that 1) NIDDK receives the resources necessary to carry out the DRWG recommendations; and 2) other institutes devote enough of their own resource to diabetes research to carry out the DRWG recommendations?

Dr. Kirschstein: After the NIH receives its appropriation, the NIDDK determines the size and scope of diabetes research that is continued, expanded, and newly initiated, working within the funds provided and relying in large part on the scientific recommendations in the DRWG Strategic Plan for program development. For example, the NIH has used existing funding to initiate and expand the diabetes research consortia, providing networks of investigators who are well-positioned to effectively employ new resources as they become available. We now have such networks in place in each of the five critical areas identified by the DRWG. In addition, we have deployed new resources to attract new investigators to diabetes – both talented newly-trained scientists and established scientists with expertise in technologies applicable to diabetes. As additional resources become available, we are able to mobilize these scientists through targeted research solicitations focused on areas of opportunity identified by the DRWG. We expect that with the continued strong leadership of the NIDDK and the cooperation of other institutes and centers, we will realize many of the scientific goals and objectives delineated by the DRWG, within the context of available budgetary resources and our responsibilities to conduct and support research on the wide array of diseases affecting the American public.

Research on diabetes and its complications spans the many institutes and centers (ICs) of the NIH. Diabetes initiatives implemented over the past several years have been largely framed within an NIH-wide context based on the scientific recommendations in the DRWG's Strategic Plan. The NIDDK leadership maintains close contact with the ICs to encourage and mobilize their participation in trans-NIH diabetes research activities through the Diabetes Mellitus Interagency Coordinating Committee, the development of trans-NIH research solicitations, the joint sponsorship of workshops and conferences, and other mechanisms. We expect that, with the recognition that diabetes and its complications are posing an increasingly ominous health threat, this participation will be further enhanced.

TYPE 1 DIABETES RESEARCH FUNDING

Mr. Cunningham: As you know, we are in the fifth year of the initiative to double the NIH budget. These increases in funding have supported new developments in juvenile diabetes research, especially the clinical trials involving transplantation of insulin producing cells. If NIH funding does not continue at the current rate of increase, how would that impact research to treat and cure diseases such as juvenile diabetes?

Dr. Kirschstein: Research on the treatment and cure of type 1, or juvenile, diabetes has benefitted from the doubling of the NIH budget over the past five years as well as from the special funds for research on type 1 diabetes provided by the Balanced Budget Act of 1997 and the 2001 Consolidated Appropriations Act. The availability of these resources has allowed us to capitalize on many scientific opportunities by initiating major new consortia to advance type 1 diabetes research. Examples include a genetics consortium to identify genes that cause type 1 diabetes, a clinical trials network (TrialNet) to test novel methods for preventing type 1 diabetes, and a beta cell biology consortium to identify methods for growing an unlimited supply of beta cells needed for cell therapy of type 1 diabetes.

The convergence in the same year, FY 2003, of both the end of the doubling period for the NIH budget and the expiration of the special type 1 diabetes funds poses a particular challenge to maintaining the momentum of research on type 1 diabetes. The NIH is pursuing strategies for type 1 diabetes research after FY 2003. For example, we have used some of the special funds for type 1 diabetes research to support short-term pilot and feasibility grants that were ready for immediate implementation. Further, significant funding has been devoted to the creation of research infrastructure and resources, which have required large initial expenditures. Some of these, such as a repository for NOD (non-obese diabetic) mice – an important model of type 1 diabetes – have lower maintenance costs in subsequent years. Additionally, during the planning process for the use of the special funds, priority has been given to proposals for which sponsoring institutes or centers were willing to commit regularly appropriated funds beyond FY 2003. The use of this criterion should help provide continued support for many of these initiatives after the conclusion of the special funding program.

NIH RESEARCH PROGRAM GOALS

Mr. Peterson: Dr. Kirschstein, like my colleagues on the Committee, I have been very supportive of the five year effort to double the NIH budget. However, I am curious as to the breakdown of the end results of this research. In particular, would you please provide me with a figure as to the percentage of NIH funded research projects which have as their end goal the development of a new pharmaceutical agent? Furthermore, would you please provide me with a broad breakdown of the end-goals of all NIH-funded research by categories such as pharmaceutical development, gene mapping, behavior and lifestyle modification, tissue/organ development, etc.? (Please feel free to use any category differential as you see fit.)

Dr. Kirschstein: The NIH supports research that involves drug design, synthesis, screening, evaluation and drug discovery and isolation. It should be noted that there is a broad spectrum of basic research, e.g., chemistry, physics, structural biology, etc. that leads up to drug development. The areas of drug research identified above account for more than 5 percent of the number of NIH funded research projects during each of the fiscal year between 1999 - 2001.

The NIH strives to improve prevention and treatment of human disorders by maximizing support for basic biomedical research, promoting health, and better understanding of the biological and behavioral basis for disease. For purposes of the Government Performance and Results Act (GPRA), the NIH has designated the following performance goals for its research outcomes program: add to the body of knowledge of normal and abnormal biological processes and behavior; develop new or improved instruments and technologies; develop new or improved approaches for preventing or delaying the onset or progression of disease and disability; develop new or improved methods for diagnosing and treating disease and disability.

Beginning in FY 2002, the NIH also identified the following subgoals, which are representative, but not inclusive, of NIH's research program. NIH will begin reporting on these subgoals in FY 2003: 1) Discover innovative approaches for identifying and measuring genetic and environmental factors that contribute to common, complex diseases across populations; 2) Develop model systems (animal models, cell lines, etc.) that will advance our understanding of disease processes; 1) Develop new technologies to enable greater understanding of genomic and proteomic information; 2) Develop biocompatible materials for use in replacing or repairing damaged and non-functioning or missing tissue; 1) Identify modifiable risk factors for disease/disability; 2) Identify, develop, and test new/improved medications for the prevention of disease/disability; 1) Develop and apply powerful new imaging, genetic, and biological technologies to enable early and more precise diagnosis and intervention; and 2) Identify and apply knowledge about factors, including gender, race, ethnicity, and socioeconomic status, to improve diagnostic reliability and treatment response.

MENTORED CLINICAL RESEARCH SCHOLARS

Mr. Peterson: Dr. Vaitukaitis, I have a question concerning the National Center for Research Resources' Mentored Clinical Research Scholar Program Award, otherwise known as K12. A request for application for the award published last November cited a pressing need to train independent patient-oriented clinical investigators and limited eligibility to candidates holding a clinical doctorate. However, applicants holding a clinical doctorate in the field of optometry were excluded from the process.

It is my understanding that schools and colleges of optometry have a history of competing for and successfully completely K training grants awarded by the National Eye Institute and other NIH institutions, and that it is unusual for a particular doctoral class of investigators to be excluded from applying for a NIH training award.

Dr. Vaitukaitis, was there a particular reason why doctors of optometry were excluded from applying under this program?

Dr. Vaitakiatis: The NCRR K12 program was promulgated in response to the Public Health Improvement Act, Title II, Clinical Research Enhancement (H.R. 2498-12). In developing the NCRR K12 program, we were guided by the NCRR authorization as a non-categorical Center. That is, we only support activities that encompass multiple specialties (for example, neurology in addition to endocrinology and immunology and urology). Activities restricted to a single discipline (optometry, in this case) are not supported by NCRR because that is supported by the categorical institutes.

MULTI-YEAR FUNDING OF RPGs IN FY 2003

Mr. Obey: The Administration's budget proposes appropriations language authorizing NIH to obligate in FY 2003 the full multi-year cost of grants and contracts awarded in that year, rather than funding these grants and contracts one year at a time. What specific plans does NIH have to make use of that new authority, if granted? What would be the effect on the estimates contained in the NIH budget justifications regarding the numbers and dollar amounts of research project grants and other grants and contracts to be awarded in FY 2003?

Dr. Kirschstein: The Congressional Justification materials submitted with the NIH budget request do not assume additional uses in FY 2003 beyond the types of multi-year awards currently employed by NIH. However, having this authority enacted by the Congress this year would provide NIH additional flexibilities in considering options for managing our resources effectively, providing stable and predictable support for new research ideas, and ensuring priorities can be funded in the outyears.

The mechanism tables that accompanied NIH's budget request for FY 2003 do not assume substantial additional uses of this multi-year funding authority beyond the types of multi-year awards currently employed by NIH. If this full funding authority is permitted to be used int eh outyears, the effects would be dependent on multiple variables, including dollar amounts for new and competing grants. Full funding of all years of a grant upfront would increase funding for outyear costs in the first year and reduce NIH's outyear commitments for non-competing grants in future years. If this authority is enacted, to determine whether to use it, NIH would consider the balance of support for ongoing research and new ideas in all mechanisms to produce the best mix for maximizing the breadth and depth of the NIH research portfolio.

SUCCESS RATE

Mr. Obey: Environmental health research is a very important part of the NIH mission, and I am concerned that the Administration's FY 2003 budget may be shortchanging researchers working in that field.

According to the budget justifications, the Administration's proposal is projected to cause the number of new and competing research grants at NIEHS to decrease by 25 percent between FY 2002 and FY 2003, and to cause the total number of research project grants at NIEHS to decrease by 8 percent - at the same time the number of research project grants at NIH as a whole is rising. In FY 2002 the estimated 27 percent "success rate" for NIEHS grant applicants is already below the NIH-wide average. However, the budget justifications indicate that the President's proposal would produce a steep drop in this rate, to 21 percent, in FY 2003.

With a 16 percent funding increase being proposed for NIH as a whole, why does the Administration's budget propose a reduction in the number of research project grants at NIEHS and a sharp decline in the success rate for NIEHS grant applications? How can we be assured that the budget provides sufficient resources to continue and expand important work in the environmental health field?

Dr. Kirschstein: In order to take advantage of new technologies and approaches to fund important initiatives such as toxicogenomics research, asthma research, the Sister Study, clinical research, and Parkinson's disease research, the NIEHS is using a variety of mechanisms other than single project R01 grants. Many of these initiatives are instead being funded through the R&D contracts mechanism. While this results in a short-term decline in the success rate, NIEHS believes that the impact of these new programs will be substantial and in some cases provide information that will be crucial for future investigator-initiated, hypothesis-driven research projects.

NIEHS is placing highest priority on those areas which are likely to yield payoffs in terms of identifying the environmental components of diseases such as Parkinson's disease, asthma, and breast cancer, and to capitalize on new approaches to identify environmental hazards and susceptible segments of the population. There are obviously many opportunities for an institute with a mission and research portfolio as broad as that of NIEHS. In order to make sure the Institute addresses as many of those as possible, NIEHS is leveraging its resources with those of other agencies, such as the U.S. Environmental Protection Agency and the Agency for Toxic Substances and Disease Registry, and other institutes within the NIH. In this way, NIEHS feels that it can expand its impact in the field of environmental health.

ETHICAL, LEGAL AND SOCIAL IMPLICATIONS OF THE HUMAN GENOME PROJECT

Mr. Obey: I understand that the National Human Genome Research Institute continues to support a program to examine the ethical, legal, and social implications of genetic research. Has this program led to any findings with respect to genetic discrimination and the confidentiality of medical information? Please describe the most significant results of this research thus far. Are these findings being disseminated to relevant federal agencies and other appropriate policy or decision makers?

Dr. Kirschstein: The National Human Genome Research Institute has a deep commitment, to analyze and address these and other important ethical, legal and social implications of new genetic information and genetic technologies. In fact, the NHGRI created the Ethical, Legal, and Social Implications (ELSI) Program to catalyze and support research in just such issues. Developing policy options to safeguard the privacy and fair use of genetic information is a priority of this program. In the mid 1990s, the NHGRI-DOE Ethical, Legal and Social Implications (ELSI) Working Group and the National Action Plan on Breast Cancer (NAPBC) cosponsored workshops on genetic discrimination in health insurance and the workplace. The findings and

recommendations of the workshops were published in Science (Hudson, Kathy, et al, "Genetic Discrimination and Health Insurance: An Urgent Need for Reform," Science, Vol. 270, 391-93, 20 October, 1995; and, Rothenberg, Karen, et al, "Genetic Information and the Workplace: Legislative Approaches and Policy Challenges," Science, Vol. 275, 1755-57, 21 March, 1997.). They have served as the foundation for policy making in the Executive branch and for many bills and enacted legislation at both the state and federal level.

Genetic discrimination, and the fear of potential discrimination, threaten both society's ability to use new genetic technologies to improve human health and the ability to conduct the very research we need to understand, treat, and prevent genetic disease. The challenge, and it is a formidable one, is to nurture scientific exploration, encourage the translation of these new discoveries into life-saving medicines, and to put in place public policies reflective of our core American values that prevent the unjust, unfair, and discriminatory use of genetic information.

The groundwork carried out by NHGRI and its partners has led to increasing recognition of the problem of genetic discrimination. That is reflected by the introduction of several bills on this topic, the holding of Congressional hearings, the signing of an executive order banning genetic discrimination in the federal work place and a statement on the topic by President Bush on June 23 during his weekly radio address. He said in part, "Genetic discrimination is unfair to workers and their families. It is unjustified. To deny employment or insurance to a healthy person based only on a predisposition violates our country's belief in equal treatment and individual merit. In the past, other forms of discrimination have been used to withhold rights and opportunities that belong to all Americans. Just as we have addressed discrimination based on race, gender and age, we must now prevent discrimination based on genetic information."

The NHGRI ELSI program has funded more than 260 projects many of which have produced significant results. Much of this work was done hand-in-hand with other parts of the NIH and other agencies of the federal government and has been distributed widely to appropriate policy makers on both the state and federal level. Below are two highlights of this research portfolio.

Cancer Genetics Studies Consortium

In 1994, in anticipation of the discovery of a number of genes and genetic mutations associated with the development of cancer, the NHGRI ELSI program funded work to stimulate the study of issues surrounding genetic testing and counseling for heritable breast, ovarian, and colon cancer risks. To promote collaboration among the individual research projects funded as a result of this initiative, to reduce duplication of effort, and to promote synergy among the projects, NHGRI sponsored the formation of a research collaboration: the Cancer Genetics Studies Consortium (CGSC).

The CGSC initially consisted of 15 independent teams that began meeting annually in 1994. Five new projects joined in 1997 and 1998, resulting in an even greater impact in the clinical integration area. In addition to more than 75 individual peer-reviewed articles published by the principal investigators, consortium members jointly produced several consensus papers. For example, three papers on informed consent procedures for cancer genetic testing and on follow-up recommendations for individuals with inherited predispositions to colon, breast, or ovarian cancer were published in the Journal of the American Medical Association (JAMA). Each of these articles has been heavily cited; a search of the Web of Science Cited Reference Search engine reveals more than 285 citations alone for the consensus article by Wylie Burke et al. regarding follow-up care for individuals with a genetic predisposition to breast cancer in the March 26, 1997 issue of JAMA. A fourth joint paper regarding more general ethical, legal, and health policy issues in cancer susceptibility testing was published in 1997 in the Journal of Law, Medicine and Ethics. In April 1999, an entire issue of the journal Cancer Epidemiology, Biomarkers, and Prevention, was devoted to cancer genetics, highlighting research in ethical, legal, and social issues for an important research community. This journal issue included nine new papers summarizing some of the initial results of the CGSC projects.

Hereditary Hemochromatosis Workshop and Population Screening Study

Hereditary Hemochromatosis (HH) is a genetic disorder of iron storage that is readily treatable but often missed. In March of 1997, the NHGRI and the Centers for Disease Control and Prevention sponsored a workshop to examine implications of the discovery of the gene (HFE) that causes HH and the possibility of widespread population testing for variants in this gene. The consensus of individuals attending the meeting was that genetic tests for HFE mutations should not be used in population screening at that time and that research to study iron overload and HH was needed. An article detailing the conclusions appeared in the July 8, 1989 issue of JAMA (Wylie Burke et al. "Hereditary Hemochromatosis: Gene Discovery and Its Implications for Population-Based Screening." JAMA. 1998;280:172-178).

In February 2000, NHGRI and the National Heart, Lung, and Blood Institute (NHLBI) awarded contracts to five field centers (Howard University, University of Alabama, University of California at Irvine, Kaiser Northwest-in conjunction with Kaiser Hawaii, and London Health Sciences Center in Ontario, Canada), a central lab (University of Minnesota), and a coordinating center (Wake Forest) to study iron overload and HH in diverse populations. This $32 million, 5-year effort is the first large scale study to examine this disorder in both majority and minority communities.

The project will: 1) identify individuals with iron overload and those with a genetic "risk state;" 2) estimate penetrance (the proportion of those with increased genetic risk for HH who actually develop symptoms due to iron overload); 3) examine genetic and other factors that contribute to iron overload in diverse communities; 4) assess ethical, legal and social issues surrounding the possibility of genotypic vs.

phenotypic screening. Ultimately, this project will provide considerable empirical information about whether phenotypic or genotypic screening for HH, or both, should be implemented on a more widespread basis. This will be of profound importance for public health.

INCREASED FUNDING IN RESEARCH AND DEVELOPMENT CONTRACTS

Mr. Obey: The NIH budget justifications indicate a very large increase in expenditures under research and development contracts in FY 2003. This would follow a large increase in FY 2002. Please provide a general breakdown of the estimated numbers and amounts of contracts in FY 2002 and FY 2003 by type or purpose, and indicate how the proposed FY 2003 increase would be used.

Dr. Kirschstein: The NIH awards research and development (R&D) contracts to non-profit and commercial organizations for scientific inquiry directed toward particular areas of research and development. Their purpose is to utilize advances in knowledge and technology to search for solutions to specific questions. R&D contracts are also used to acquire research-related services. For example, clearinghouses which provide disease-related information to the public, such as the Alzheimer's Disease Education and Referral clearinghouse or the National Digestive Diseases and Diabetes Information clearinghouses, are supported by R&D contracts. Contracts are used for patient recruitments into clinical trials, and for vaccine development efforts, in HIV, for example.

Funding for research and development contracts increases by close to 30 percent in FY 2002, and by nearly 45 percent in FY 2003. These larger increases in R&D contracts, as compared to other extramural mechanisms, are driven by several factors.

The FY 2002 increase includes $28 million to support the two new loan repayment programs (LRPs)–the Extramural Clinical Research LRP, and the Extramural Pediatric Research LRP. Each individual who will participate in these programs signs a contractual agreement with NIH regarding loan repayment by the government. The FY 2003 President's budget request nearly doubles these contract programs by providing $25 million over the FY 2002 estimate.

The threat of bioterrorism became a reality in the United States with the intentional delivery of anthrax spores through the mail and through print media and television and government offices. A large portion of the NIH increased bioterrorism activities will be supported through R&D contracts. Included as part of the R&D contracts increase within NIAID in FY 2003 is an additional $225 million over the FY 2002 amount of $43 million to support the Administration's initiative to develop biomedical research tools to detect, diagnose, prevent and treat infections by biological agents that could serve as possible weapons. The FY 2003 President's budget request also includes $250 million for anticipated procurement of anthrax vaccines currently under development and testing.

In the FY 2003 President's budget request, a total of $49 million is directed toward collaborative research projects with the Department of Defense, including development of an HIV/AIDS vaccine, research into the use of free electron lasers for surgical debridement, and research into radiation treatment.

The FY 2003 President's budget request will allow NIH to continue its FY 2002 support of $100 million for the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis, to further the NIH's efforts to prevent and alleviate these diseases. The full $100 million would be funded through R&D contracts in FY 2003.

Funding for AIDS vaccine research through R&D contracts would increase by $22 million in the FY 2003 President's budget request, bringing the total to $63 million.

NIH is mandated to support small businesses conducting research and development projects that may lead to commercial products or services. A set-aside of 2.5% for the Small Business and Innovation Research program (SBIR) and 0.15% for the Small Business Technology Transfer Research (STTR) program determines the minimum funding level. This program is funded by R&D contracts as well as grants and $2 million of the increase in R&D contracts is accounted for by this set-aside.

OFFICE OF LOAN REPAYMENT AND SCHOLARSHIP

Mr. Obey: Please provide information on scholarship and loan repayment programs at NIH for each of fiscal years 2001, 2002, and 2003, including (for each program) the actual or proposed funding levels, the number of scholarships or loan repayment contracts awarded or to be awarded, and (to the extent available) the number of applications received.

Dr. Kirschstein: In fiscal year 2001, the intramural Undergraduate Scholarship Program (UGSP) provided scholarship awards and funding for individuals performing their one-year service payback in the amount of $635,000 for 12 undergraduate students and 7 graduate students. There were 52 applicants for the program. In fiscal year 2002, the projected funding level for the UGSP is $1,190,000, with a projected total of 15 scholarship awards and 15 service payback contracts. In fiscal year 2003, the projected funding level for the UGSP is $815,000, with a projected total of 15 scholarship awards and 12 service payback contracts.

In fiscal year 2001, the intramural AIDS Loan Repayment Program (LRP) had a funding level of $718,000. There were 15 contracts awarded during the fiscal year, and there were 15 applicants for the program. In fiscal year 2002, the projected funding level for the AIDS LRP is $1,125,000, with a projected total of 20 contracts. In fiscal year 2003, the projected funding level for the AIDS LRP is $1,500,000, with a projected total of 20 contracts.

In fiscal year 2001, the intramural Clinical Research LRP had a funding level of $1,255,000. There were 21 contracts awarded during the fiscal year, out of 22 applicants for the program. In fiscal year 2002, the projected funding level for the Clinical Research (Intramural) LRP is $1,332,000, with a projected total of 24 contracts. In fiscal year 2003, the projected funding level for the Clinical Research (Intramural) LRP is $1,459,000, with a projected total of 24 contracts.

In fiscal year 2001, the General LRP had a funding level of $3,118,000. There were 48 contracts awarded during the fiscal year, and there were 48 applicants for the program. In fiscal year 2002, the projected funding level for the General LRP is $1,490,000, with a projected total of 38 contracts. In fiscal year 2003, the projected funding level for the General LRP is $1,653,000, with a projected total of 30 contracts.

In fiscal year 2001, the Contraception and Infertility Research LRP had a funding level of $976,579. There were 16 contracts awarded during the fiscal year, and there were 20 applicants for the program. In fiscal year 2002, the projected funding level for the Contraception and Infertility LRP is $1,200,000, with a projected total of 18 contracts. In fiscal year 2003, the projected funding level for the Contraception and Infertility LRP is $1,500,000, with a projected total of 20 contracts.

In fiscal year 2001, the Clinical Researchers from Disadvantaged Backgrounds (Extramural) LRP had a funding level of $1.38 million. There were 17 contracts awarded during the fiscal year, and there were 24 applicants for the program. In fiscal year 2002, the projected funding level for the Clinical Researchers from Disadvantaged Backgrounds (Extramural) LRP is $1.95 million, with a projected total of 25 contracts. In fiscal year 2003, the projected funding level for the Clinical Researchers from Disadvantaged (Extramural) LRP is $2.06 million with a projected total of 27 contracts.

In fiscal year 2001, the Health Disparities Research LRP had a funding level of $1.83 million. There were 28 contracts awarded during the fiscal year, and there were 78 applicants for the program. In fiscal year 2002, the projected funding level for the Health Disparities Research LRP is $2.03 million, with a projected total of 30 contracts. In fiscal year 2003, the projected funding level for the Health Disparities Research LRP is $2.90 million, with a projected total of 35 contracts.

Fiscal year 2002 is the first year for the Clinical Researchers (Extramural) LRP. The projected funding level for the Clinical Researchers LRP is $22,552,000, with a projected total of 225 contracts. In fiscal year 2003, the projected funding level for the Clinical Researchers LRP is $43,335,000, with a projected total of 428 contracts.

Fiscal year 2002 is the first year for the Pediatric Research LRP. In fiscal year 2002, the projected funding level for the Pediatric Research LRP is $5,115,000, with a projected total of 51 contracts. In fiscal year 2003, the projected funding level for the Pediatric Research LRP is $9,644,000, with a projected total of 96 contracts.

SAMHSA AND NIH

Mr. Obey: The President's budget proposes a 23 percent reduction in funding for the Center for Substance Abuse Prevention within the Substance Abuse and Mental Health Services Administration (SAMHSA), with this reduction coming largely in the area of applied research. Budget documents and testimony to this committee indicate that a rationale for the reduction at SAMHSA is that this type of research is more appropriately undertaken at NIH.

How much overlap now exists between research programs at SAMHSA and at NIH? What specific steps does NIH plan to take to make up for the proposed reduction at SAMHSA and to take on research functions now being performed there - particularly research into substance abuse prevention strategies and methods?

Dr. Kirschstein: As part of an effort to strengthen both the research and service missions of the Federal Government, a comprehensive and important bipartisan legislation reorganized the former ADAMHA in 1992 [P.L. 102-321]. The three research entities of ADAMHA - NIMH, NIAAA, and NIDA – were merged into the NIH. This legislation mandated that the three Institutes obligate at least 15 percent of their research budgets for health services research. The service-oriented arms of ADAMHA became the current Substance Abuse and Mental Health Services Administration (SAMHSA). Over time, SAMHSA has developed its own portfolio of knowledge development grants. As a result, both agencies have been involved in health services research to examine factors around the delivery of health services, including research on implementing evidence based practices in real world settings.

The mission of the NIH institutes is to lead the Nation in bringing the power of science to bear on their respective areas of research. This charge has two critical components: first, the strategic support and conduct of theoretically driven research across a broad range of disciplines including health services research, and second, to rapidly and effectively disseminate the results to improve treatment and prevention. SAMHSA's mission is to improve the quality and availability of prevention, treatment, and rehabilitative services in order to reduce illness, death, disability, and cost to society resulting from substance abuse and mental illnesses.

NIAAA, NIDA, and NIMH each work closely with SAMHSA on a number of specific critical issues. For example,

- NIAAA and SAMHSA are working together on college drinking, underage and adolescent drinking, fetal alcohol syndrome, and the effects of alcohol advertising on youth.

- In keeping with its research mission, NIDA researchers recently have developed a new medication for treating opiate addiction (buprenorphine and buprenorphine combined with naloxone). NIDA continues to work with

SAMHSA and other federal agencies, such as FDA, to develop a strategy to ensure that new treatments such as buprenorphine are accessible to those in need of treatment.

- The NIMH has a well-developed program in services research that started prior to its joining the NIH. This program sponsors research on topics including the cost-effectiveness of specific mental health treatments, the economic impact of mental disorders, innovative models for assessing and treating mental illness in primary care settings, and research on ways to increase the adoption of appropriate mental health services in every day clinical settings. NIMH has collaborated with SAMHSA to fund research on its demonstration projects; in these efforts, NIMH pays for the research component while SAMHSA funds the delivery of services.

In each instance, research findings from NIAAA, NIDA, and NIMH are seen to provide a foundation for many of SAMHSA's programs. To the extent possible, we at NIH collaborate with our colleagues at SAMHSA to ensure that research is disseminated to the field.

In line with the FY 2003 Budget, NIH and SAMHSA will continue meeting to collaborate more fully in mental health and substance abuse prevention and treatment and better clarify the roles of each agency. This increased collaboration is critical to shorten the time period between research advancements and improvements in the delivery of services.

NIAAA, NIDA, and NIMH are in the process of obtaining a list of all current SAMHSA grantees. The Institutes intend to send notices of all of their funding opportunities (Requests for Applications, Requests for Proposals, and Program Announcements) to SAMHSA's grantees, to encourage them to apply for NIH grants.

The Institutes will invite SAMHSA grantees to NIH workshops, conferences, symposia, and other meetings that will help them develop NIH grant applications. NIAAA, NIMH, and NIDA will host a technical-assistance workshop, in the Fall of 2002, to improve SAMHSA grantees' skills in applying for NIH prevention, treatment, and health-services research grants.

With respect to substance abuse prevention strategies and methods, NIDA's prevention portfolio is particularly robust and has provided communities across the country with science-based prevention principles and strategies that can be used to assess local drug abuse problems and to develop comprehensive, effective drug abuse prevention strategies. To take this prevention research to the next level so as to ensure the successful implementation of science-based interventions in communities and to address some new unstudied tough questions that focus, for example, on the more immediate factors that influence an adolescent's decision to use or not use drugs, NIDA has just launched a new National Prevention Research Initiative (NPRI). The NPRI

will involve a number of partners working together to test the effectiveness of new and existing science-based prevention approaches in different communities, while simultaneously studying how best to adapt the programs for local communities. Another component of this Initiative will consist of transdisciplinary prevention research centers, which will foster collaborations between neuroscientists, behavioral scientists, cognitive scientists, and researchers on drug abuse prevention to address knowledge gaps and how to approach the scientific questions. The NIH leadership will dialogue with SAMHSA leadership in determining which interventions are ready for implementation at the community level and also to determine areas that need more research before they can be recommended for implementation.

This multi-faceted approach will bring together researchers from a variety of disciplines as well as state and local policy makers to work together to more thoughtfully and innovatively bring science-based interventions to the community level. NIDA encourages potential grantees who may have participated or have gained expertise while being supported by SAMHSA's Center for Drug Abuse Prevention to apply for NIDA funding or to establish relationships with NIDA researchers. NIDA also will provide technical assistance to develop SAMHSA grantees' research capabilities and grant writing skills. Grantees with expertise on how best to deliver prevention services to comminutes will be useful to our Nation's prevention endeavors.

HIV VACCINE RESEARCH PROGRAM

Ms. Pelosi: It is my understanding that the Administration has decided to move the well regarded military HIV vaccine research program to the NIH. Could you tell us about why this transfer is being made? Will the funding and staffing of the DOD vaccine program be maintained at NIH? Will you move forward with the Phase 3 clinical trial that DoD has planned for Thailand?

Dr. Kirschstein: The oversight and management for the DoD HIV Research and Development Program of the U.S. Army Medical Research and Material Command (USAMRMC) will be transferred to the NIH. NIAID, which has the primary responsibility for HIV/AIDS research within the NIH, will assume responsibility for this program beginning October 1, 2002.

DoD's HIV/AIDS Research program is consistent with NIH's mission to support and conduct research to understand, treat, and prevent diseases that threaten millions of human lives. For many years, the National Institute of Allergies and Infectious Diseases has supported and conducted research on diseases that transcend national boundaries. DoD's HIV/AIDS program has focused primarily on the diagnosis of HIV/AIDS, natural history of the progression of the disease, epidemiology, studies of drug resistance and vaccine development, and preclinical trials, all of which are complementary to NIH's HIV/AIDS research portfolio.

USAMRMC's experience conducting international drug and vaccine development and testing and their established collaborative ties in many parts of the world will enhance NIAID's expanding international efforts. In turn, USAMRMC programs will benefit from NIAID's vast HIV/AIDS pre-clinical research program, which is integrated into NIAID's comprehensive HIV/AIDS effort.

Since 1993, NIAID and USAMRMC have collaborated frequently on complementary research programs. The two Institutes are collaborating on a large international clinical trial of IL-2 in people infected with HIV. By formally integrating the experience, expertise, research infrastructure and resources of both Institutes, the merger will ensure the U.S. government HIV research effort is comprehensive, efficient and coordinated.

During Fiscal Year 2003, NIAID will continue to fund and support operations of the current USAMRMC HIV Vaccine research program, including the Phase III HIV vaccine efficacy trial in Thailand that is scheduled to commence later in 2002. We will continue to move forward with the clinical trials in Thailand.

HUMAN EMBRYONIC STEM CELL LINES

Ms. Pelosi: As you know, many scientists in the research community are very concerned that the limitations President Bush has placed on stem cell research will seriously constrain the development of new medical treatments.

Specifically, the restriction to lines that were developed before the President's speech on August 9th has raised many questions.

Has the NIH produced a list of the existing lines that President Bush said are available?

Have any of the existing lines proved unusable?

Is there sufficient genetic diversity in the existing lines to ensure that stem cell therapies are useful to all populations?

Has adequate consent from the embryo's donors been obtained for all the lines?

Can you assure that university and government scientists will have adequate access to these lines, which are controlled by a small numbers of companies and laboratories around the world?

Dr. Kirschstein: The NIH Registry is available on our website and lists all of the approved lines. We have added six cell lines since the original posting of this Registry. None of the existing lines has proved unusable, but it is very early in the research to be able to speak about the comparative advantages or disadvantages of different lines. We do not know the genetic background of all of the donor(s) that led to the establishment of the cell lines. In fact, several of them were developed anonymously. The cell lines were derived in at least 5 different country which provides some background about the genetic diversity.

In each case the sources of the stem cells provided documentation of the informed consent process used in obtaining the lines.

NIH is taking several steps to facilitate investigator access to stem cell lines. These cell lines are in various stages of development and some of the providers are not sufficiently prepared to provide them for research use. Therefore, NIH developed research infrastructure awards that provide resources to the owner of the cell lines to hasten their development and characterization. Many of the sources have commercial development interests and the use of those cells requires the source to obtain a license from the patent holder, WiCell. Inc. NIH is also working with the sources of the embryonic stem cells to develop memoranda of understanding with the NIH that will facilitate access to the cells.

OAR PLANNING AND BUDGET AUTHORITY

Ms. Pelosi: The Office of AIDS Research has been a model for coordinating disease specific research across Institutes and Centers. We know how much more work there is to be done in this area, including the development of a vaccine and treatments that are more effective and cause fewer side effects. Does the OAR continue to have the strategic planning and budget authority necessary to coordinate the AIDS research portfolio across the NIH?

Dr. Kirschstein: Yes, the OAR continues to be a model for trans-NIH research coordination. OAR coordinates the scientific, budgetary, and policy elements of the NIH AIDS program, supported by nearly every Institute and Center; prepares an annual comprehensive trans-NIH plan and budget for all NIH-sponsored AIDS research; facilitates NIH involvement in international AIDS research activities; and identifies and facilitates scientific programs for multi-institute participation in priority areas of research. The legislative authorities of the Office of AIDS Research allow NIH to pursue a united research front against the global AIDS epidemic.

The OAR develops the annual comprehensive NIH Plan for HIV-Related Research that is based on the most compelling scientific priorities that will lead to better therapies and prevention strategies for HIV infection and AIDS. The AIDS Research Plan serves as the framework for developing the annual NIH AIDS budget; for determining the use of NIH AIDS-designated dollars; for tracking and monitoring expenditures; and for informing the scientific community, the public, and the AIDS-affected community about NIH research priorities. The Plan establishes the NIH AIDS scientific agenda for the Scientific Areas of Emphasis of AIDS research: Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral and Social Science. As the epidemic expanded, OAR recognized the need to take a planning approach that cross-cut these scientific areas. Thus, the Plan also addresses the critical cross-cutting areas of Racial and Ethnic Minorities; Women and Girls; Microbicides; Prevention; International Research; Training, Infrastructure, and Capacity Building; and Information Dissemination.

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

OFFICE OF LOAN REPAYMENT AND SCHOLARSHIP

Ms. Pelosi: I am very pleased that the NIH is moving forward with the Loan Repayment Program for Clinical Researchers as authorized by the Clinical Research Enhancement Act. I am also pleased that the President's budget would double the program's funding for FY2003. However, I have several questions regarding NIH policies with respect to this program:

In the first year, only researchers with NIH support were eligible to apply. The Clinical Research Enhancement Act did not intend to disenfranchise trainees and other clinical investigators who fund their research outside of NIH. The September 6 announcement stated that NIH will expand the program eligibility after the first year. When will the details of this expansion be announced?

Dr. Kirschstein: In fiscal year 2002, the first year of the Clinical Research Loan Repayment Program, the eligibility criteria were designed to allow for the smooth implementation of several Loan Repayment Programs concurrently, using an innovative electronic web-based application process, and to provide a starting point to gain insight into the size and nature of the applicant pool. We are using knowledge gained from this pool of applicants to enhance the process so that we are able to communicate more effectively with a larger and more diverse pool in future years.

Beginning with fiscal year 2003, the eligibility criteria will be expanded to include individuals whose research is supported by foundations, professional societies, and other non-profit sources.

The details of the program expansion will be announced in the *NIH Guide to Grants and Contracts* and on our Internet home page (www.lrp.nih.gov) no later than May 2002. In addition, we will present information about the programs as widely as possible in other venues, such as the annual meetings of professional associations and at educational institutions.

Ms. Pelosi: I know that the application deadline for the first year of this program has just passed. What was the total number of applications received? I would appreciate it if you would provide additional demographic information for the record including a breakdown of the applicants by the category of NIH support they receive as well as the average tuition loan debt of applicants in each category.

Dr. Kirschstein: The Loan Repayment Program for Clinical Researchers has generated considerable interest in the medical and research communities. We have received 487 applications to the Clinical Research Loan Repayment Program this fiscal year. We expect to provide these to the appropriate NIH Institutes and Centers for review during the first week in April 2002.

The NIH received 487 Clinical Research Loan Repayment Program applications this fiscal year. Of these, 5.14% receive funding under a National Research Service Award for Postdoctoral Fellows (F series), 36.42% receive funding under an Institutional Research Training Grant (T series), 38.27% receive funding under an NIH Career Development Award (K series), 15.64% receive funding under a Research Grant (R series), 2.67% receive funding under a Research Program Project Grant (P series), and 1.85% receive funding under a Research Project Cooperative Agreement (U series).

The racial and ethnic composition of the applicant pool for the Clinical Researchers Loan Repayment Program is 68.41% Caucasian, 11.27% Asian, 6.24% African-American, 3.02% Latino, 0.6% American Indian or Alaskan Native, 0.6% Native Hawaiian or Other Pacific Islander, and 8.85% reported "other" or did not respond. Female applicants constitute 41.68% of this pool, male applicants constitute 54.62% of the pool, and 3.7% did not respond.

STEM CELL RESEARCH AND THERAPEUTIC CLONING

Ms. Pelosi: As you know, once we learn how to make embryonic stem cells differentiate into, for example, brain tissue for people with Alzheimer's or Parkinson's disease, we must ensure that the body will not reject these stem cells when they are implanted.

This is a very real concern because transplanted organs or tissue are rejected when the body identifies them as foreign. In a report on stem cell research released by the National Institutes of Health last June, the NIH described therapeutic cloning's potential to create stem cell tissue with an immunological profile that exactly matches the patient. This customized therapy would dramatically reduce the risk of rejection.

I understand that embryonic stem cell research can go forward without therapeutic cloning. However, won't the ability of patients to benefit from stem cell research be negatively impacted if a ban on therapeutic cloning were enacted?

Dr. Kirschstein: Cloning refers to any process that results in the creation of an identical or nearly identical genetic copy of a molecule, cell, or individual plant, animal, or human. Somatic cell nuclear transfer (SCNT) is a cloning technique used by scientists to produce a nearly genetically identical copy of an existing organism or cells or tissues from that organism. So-called human "therapeutic" cloning would employ SCNT with the express purpose of creating cells and tissues that are nearly genetically identical to the individual who donated the somatic cell from which the genetic material was obtained. In theory, if transplanted, such tissues would be less likely to result in graft v. host disease and would not be rejected.

The Administration is, however, opposed to any form of human cloning using SCNT, including so-called "therapeutic" cloning for the purposes of producing human cells or tissues.

MAMMOGRAPHY

Mrs. Lowey: Dr. Kirschstein, I would first like to thank you for your service. You have provided great leadership to NIH at a critical time. I think I speak for all my colleagues in giving you our best wishes in the future.

My first question is on the issue of mammography. As you know, recent studies have raised questions about the data used to determine whether early detection leads to better outcomes. I was glad to see NIH join with Secretary Thompson in reaffirming the recommendation that women should still undergo an annual mammogram after age 40. It is important that women have all the facts about the procedure, but also that they understand that it is the best tool we have right now to detect breast cancer early.

However, I think that the current debate over the data on mammography misses the point. I think it's time for the next generation of early detection. I know that researchers across the country are looking at promising new methods. Despite these advances, even the new technologies have glaring shortcomings. Experts and scientists agree that we still have not found the 21st century early detection method we need.

I believe that we must substantially increase and accelerate research into these and other breast cancer screening techniques. What do you think the next steps will be? What leadership will NIH provide in this area?

Dr. Kirschstein: The NCI is taking a very active role in both improving on currently available technology as well as developing new methods for the early detection of breast cancer.

Digital mammography is similar in many ways to conventional (film-screen) mammography except that the image is captured on an electronic receptor (also called a detector) instead of on film. The electronic receptors capture more information than film. The electronic image can be processed in a variety of ways by computer software, and pilot data suggest that this computerized image processing will result in detection of more cancers and elimination of more false positives than occur in conventional mammography. Furthermore, software can be used to automatically detect suspicious areas on the mammogram and call these to the attention of the radiologist. This should result in more consistent interpretation of mammograms and fewer missed cancers.

Different manufacturers use different technologies for their electronic detectors, and it is not yet clear whether they are all equal to each other and better than conventional mammography. Two technologies have been approved by the FDA, and two others are available in test units at several sites in the United States. NCI is funding a large trial comparing digital mammography with conventional mammography. Technologies from four different manufacturers are included. The trial will accrue approximately 49,000 women at 19 sites in the United States over 2 years. Results should be available in approximately 3 years.

There are several imaging technologies that are being studied or proposed as alternatives or adjuncts to mammography for early detection of breast cancer. Two imaging technologies that are relatively mature and have been suggested for early breast cancer detection are ultrasound and MRI. NCI is funding a cooperative group of fourteen institutions doing a pilot study of MRI for early breast cancer screening in women at high risk. That pilot study is almost complete and results are expected within a year or two. Pilot studies of ultrasound for breast cancer detection have been completed and show some promising results, although somewhat dependent on the experience of the people doing the ultrasound testing, NCI funds a cooperative group for multicenter imaging clinical trials called the American College of Radiology Imaging Network (ACRIN). Within ACRIN there is a protocol development team putting together a proposal for a large multicenter trial of ultrasound for early breast cancer detection.

Computed tomography (CT) provides 3-dimensional images of body structure. Recent advances in CT technology make it possible to acquire CT images in seconds, and use much lower doses of radiation than previously. The potential advantage of using CT for breast imaging is that it could be done without applying compression to the breast. NCI is funding a Bioengineering Research Partnership (BRP) grant for development of a CT scanner dedicated for use to detect breast cancer that could produce 3-D images of the breast using no more radiation than is used in conventional mammography. Such a device could potentially be used for screening, and might find increased acceptance among women compared to mammography because of the absence of the need for compression.

There are several less mature imaging technologies that have been proposed or are being investigated for early breast cancer detection. Thermography is a technique that detects changes in skin temperature caused by changes in blood flow. Thermography was tested for early breast cancer detection in the 1970's but abandoned because of poor sensitivity. In recent years the FDA approved two new devices for thermography. However thermography is still not widely accepted for screening because of high false positive rates and low sensitivity. NCI is funding some investigator-initiated research projects that seek to improved thermography for breast cancer detection.

Electrical impedance devices work by passing a small electric current through the breast and measuring the voltage changes on the surface of the skin. An FDA approved device is commercially available, but is not widely used for screening because of relatively poor sensitivity and high false positive rates. For comparison, the sensitivity and specificity of ultrasound and MRI have both been better in pilot trials than the corresponding values for thermography or electrical impedance.

Nuclear medicine techniques are used to help distinguish benign from malignant breast masses, but so far have not been shown to be practical for widespread screening. Scintimammography using a radiolabeled compound called sestamibi is useful in

evaluating masses detected by mammography or by physical examination, but it is not considered useful for screening because it does not reliably detect a tumor smaller than one centimeter. Similarly, PET scanning with a radiolabeled glucose compound is useful for evaluating breast abnormalities, but is not considered useful for screening because it does not reliably detect a tumor smaller than one centimeter, and it is relatively expensive. NCI is funding some investigator-initiated research projects that aim to develop dedicated PET scanners for the breast that would make the examination considerably less expensive and would have improved resolution for finding small cancers. If these goals are achieved, then PET scanning might be a reliable screening modality.

There are a variety of optical technologies that use light from lasers in the visible spectrum or in the near-infrared spectrum. These can detect differences between oxygenated and non-oxygenated hemoglobin, or can detect signals from optical contrast agents that have been injected. These technologies are in an early stage of development and thus, it is difficult at this time to predict whether they will be feasible for screening. However some early results look very promising and optical technologies have the advantages of being relatively inexpensive and not using ionizing radiation. NCI funds several research projects looking at a variety of different optical technologies, and will soon issue a Request for Applications for a network for optical technologies development.

There are a variety of other imaging modalities which are in very early stages of development for possible detection of early breast cancer. These include technologies such as magnetic resonance spectroscopy, magnetomammography, Hall effect imaging (passing an electric pulse through tissue while exposed to a magnetic field), thermo-acoustic computed tomography, and focused microwaves for imaging. Again, NCI funds a wide variety of research projects on these imaging technologies, including a program project entitled, "Alternative Breast Cancer Imaging Modalities." It is too early to predict whether any of these will actually become useful for early breast cancer detection.

Many imaging modalities rely on the presence or absence of structural change for detecting abnormality. One of the uncertainties about a structural change is whether it represents a biologically aggressive or non-aggressive cancer. Better understanding of the biology of breast cancer is needed. As our knowledge about the biology of breast cancer improves, some of the novel imaging techniques described above that can detect functional changes may become more feasible and indicate lesions that definitely need to be removed. In the near term, it is likely that MRI and ultrasound will be found to be useful for screening certain populations of women for whom mammography is inadequate, such as young women at high risk and women with very dense breast parenchyma.

In addition to imaging technology, NCI is investing in new biologic tests to improve our ability to identify cancer cells at their earliest possible stages of development. Among the research being supported:

Molecular Analysis - NCI's Innovative Molecular Analysis Technologies Program (IMAT) supports the development of non-invasive techniques for identifying molecular changes that distinguish cancer cells from normal cells. More than 100 research projects are under way, focusing on new approaches to analyze DNA, RNA, and proteins.

Proteomics: Finding Protein Patterns - Proteomics is the systematic study of protein expression and function. In the Clinical Proteomics Program, a joint initiative of NCI and FDA, researchers are discovering differences in patterns of protein in the blood from cancer patients compared to people without cancer and applying this knowledge to early detection of breast cancer.

Biomarkers - NCI's Early Detection Research Network (EDRN) is the first comprehensive network to develop and validate early detection markers for cancer. Researchers are studying a variety of molecules, proteins, genes, and other biological substances that may be the earliest warning signs that normal cells are on the road to becoming cancerous. Their discoveries are then translated into methods for detecting warning signals, sometimes even before full-blown cancer can develop.

Finding Fingerprints of Cancer Cells: The Molecular Classification of Tumors - All cells have unique "signatures" - special characteristics related to which genes are active and which proteins or other products the cell manufactures. During the transformation of a normal cell to a cancer cell, the cell's signature changes, and the change becomes a signal of the presence of cancer. Researchers are developing profiles of molecular alterations in human tumors, such as breast cancer, using DNA, RNA, or protein-based technologies. This technology holds promise for improving the early detection, diagnosis, and treatment of cancer.

Over the years, researchers have focused on examination of cells shed by breast tissue into the ducts. Investigators have now developed techniques for collecting nipple aspirates and ductal lavage and hope that it may be possible to evaluate suspicious breast masses detected by mammography by analyzing these secretions. It may be possible to spare at least some women the need to undergo a surgical biopsy.

NCI is playing a leadership role for the Interagency Council, a newly created multi-agency group designed to serve as a sounding board for investigators and manufacturers attempting to take emerging medical imaging technology to market. It consists of a core staff from the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS) and NCI with experience and knowledge concerning the decision-making processes for their agencies to evaluate medical imaging products. Additional agency staff may be added to the core group on specific

matters when needed. The purpose of the Council is to provide multi-agency advice that may help guide imaging technology developers in the fight against cancer. The Council will provide advice on projects or project proposals brought voluntarily by investigators and technology/device developers in industry and academia. It offers a new, multi-agency perspective to the communication with government agencies that is already available to investigators and companies.

The three agencies participating in the Interagency Council all have different roles in the development of medical imaging technologies. NCI has created and is expanding a Biomedical Imaging Program. This effort currently funds innovative device and technology development, small animal imaging, in vivo cellular and molecular imaging centers, and a clinical trials imaging network (ACRIN). NCI will provide input on scientific and medical issues, information on the initiatives and research resources available to fund or develop imaging technologies, explain the process for gaining access to such resources, and facilitate future interactions of developing imaging technology with NIH staff or with other NCI-sponsored investigators.

The NCI has organized a unique Imaging Forum to bring technology developers from academia and industry together with funding agencies, regulators, and reimbursement sources. These partnerships promote communication and progress in the development, testing, and adoption of new imaging modalities and applications.

OFFICE OF LOAN REPAYMENT AND SCHOLARSHIP

Mrs. Lowey: I am pleased to see that NIH is moving forward with the Loan Repayment Program for clinical researchers. I am also glad to see that the President's budget includes a 100% increase for FY03. I have two questions about NIH policies with respect to this program.

In the first year, only researchers with NIH support were eligible to apply. The Clinical Research Enhancement Act, which I authored, did not intend to limit this program only to those receiving NIH funding, but to help advance the next generation of clinical researchers. The announcement issued last year about this program states that NIH will expand the program's eligibility after the first year. When will this expansion occur, and what will the scope of the expansion be?

And, I am aware that the application deadline for the first year of the program has just passed. How many applications did the NIH receive? Could you provide us with additional demographic information from these applications, including a breakdown of applicants by the category of NIH support they receive, as well as the average tuition loan debt of applicants in each category?

Dr. Kirschstein: In fiscal year 2002, the first year of the Clinical Research Loan Repayment Program, the eligibility criteria were designed to allow for the smooth implementation of several Loan Repayment Programs concurrently, using an innovative

electronic web-based application process, and to provide a starting point to gain insight into the size and nature of the applicant pool. We are using knowledge gained from this pool of applicants to enhance the process so that we are able to communicate more effectively with a larger and more diverse pool in future years.

Beginning with fiscal year 2003, the eligibility criteria will be expanded to include individuals whose research is supported by foundations, professional societies, and other non-profit sources.

The details of the program expansion will be announced in the *NIH Guide to Grants and Contracts* and on our Internet home page (www.lrp.nih.gov) no later than May 2002. In addition, we will present information about the programs as widely as possible in other venues, such as annual meetings of professional associations and at educational institutions.

The Loan Repayment Program for Clinical Researchers has generated considerable interest in the medical and research communities. We have received 487 applications to the Clinical Research Loan Repayment Program in FY 2002. We expect to provide these to the NIH Institutes and Centers for review during the first week in April 2002.

The NIH received 487 Clinical Research Loan Repayment Program applications this fiscal year. Of these, 5.14% receive funding under a National Research Service Award for Postdoctoral Fellows (F series), 36.42% receive funding under an Institutional Research Training Grant (T series), 38.27% receive funding under an NIH Career Development Award (K series), 15.64% receive funding under a Research Grant (R series), 2.67% receive funding under a Research Program Project Grant (P series), and 1.85% receive funding under a Research Project Cooperative Agreement (U series).

The racial and ethnic composition of the applicant pool for the Clinical Researchers Loan Repayment Program is 68.41% Caucasian, 11.27% Asian, 6.24% African-American, 3.02% Latino, 0.6% American Indian or Alaskan Native, 0.6% Native Hawaiian or Other Pacific Islander, and 8.85% reported "other" or did not respond. Female applicants constitute 41.68% of this pool, male applicants constitute 54.62% of the pool, and 3.7% did not respond.

The average educational loan debt (outstanding principal and interest) of the applicant pool for the Clinical Researchers LRP is: $80,625 for applicants with a K grant, $99,602 for applicants with a T award, $64,130 for applicants with an F award, $97,500 for applicants with a P grant, $59,012 for applicants with an R grant, and $59,652 for applicants with a U grant. These averages are tentative and will be adjusted as we continue to verify the total eligible debt of each applicant.

CLINICAL RESEARCH ENHANCEMENT ACT

Mrs. Lowey: I am also pleased that NIH has begun implementation of other programs authorized in the Clinical Research Enhancement Act. The Graduate Training in Clinical Investigation Award, however, which is intended to provide tuition and stipend support for graduate students enrolled in programs funded by NIH curriculum development grants, has not been implemented. In the past, you have referenced the NCRR Clinical Research Scholars program as an alternative. Could you please tell me how the NCRR program meets the criteria of the Graduate Training in Clinical Investigation Award? Can't we have both?

Dr. Kirschstein: NCRR will implement a new institutional career development program in FY 2002 for "individuals pursuing master's or doctoral degrees in clinical investigation" as specified in the Graduate Training in Clinical Investigation Award description. The "Mentored Clinical Research Scholar (MCRS) Award," will be awarded through the K12 mechanism. The NCRR expects to fund around 10 proposals, submitted in late February 2002. The K12 grants will support physicians or dentists to pursue master's or doctoral degrees in clinical investigation. The candidate-mentor pairs will be selected by an institutional committee. This approach will allow timely selection of candidates who will have a career development plan created to match their career goals and are eligible for the loan repayment program. The salary level ranges between $75,000 to $90,000 for a 75 to 90 percent time committment.

Having both the Clinical Research Scholars Program and the Graduate Training in Clinical Investigation Award would duplicate a support mechanism already available.

COLLABORATION ON TYPE 1 DIABETES RESEARCH

Mrs. Lowey: Juvenile diabetes impacts all major organs in the body. Because of this, virtually all NIH Institutes play a role in juvenile diabetes research. How do you ensure that all relevant Institutes collaborate to advance research to cure juvenile diabetes and treat its devastating complications?

Dr. Kirschstein: The Diabetes Mellitus Interagency Coordinating Committee (DMICC) is one route by which many NIH Institutes and Centers, along with the CDC, the FDA, AHRQ, and other HHS agencies, coordinate research on all aspects of diabetes, including type 1, or juvenile, diabetes and its complications. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the lead institute for diabetes research at the NIH, chairs this Coordinating Committee. The DMICC has been a focal point for catalyzing NIH-wide research on key issues relevant to juvenile diabetes, including the eye, kidney, and heart complications, as well as the disturbing increase in type 2 diabetes in children.

The NIDDK also steers a trans-HHS Planning and Evaluation Strategy Group that guides the use of special funds for type 1 diabetes research that were provided by the Balanced Budget Act of 1997 and the 2001 Consolidated Appropriations Act. This Planning and Evaluation Strategy Group includes representatives from multiple NIH institutes and centers, the CDC, the FDA, AHRQ, the Juvenile Diabetes Research Foundation, and the American Diabetes Association. It has met several times to identify areas of scientific importance for type 1 diabetes research. The Planning Group convened most recently in February 2001 to consider proposals for the special type 1 diabetes research funds, which were submitted by the participating NIH institutes and centers, and the other HHS agencies.

To leverage support for type 1 diabetes research, high priority has been given throughout the resource allocation process to proposals to which HHS components would commit regularly appropriated funds, proposals that cross institute or agency boundaries, and proposals that could attract new scientific talent, who have relevant experience to diabetes research.

Members of the Planning Group have also suggested the names of leading scientists to serve on external advisory panels on the use of the type 1 diabetes funds. One such panel met in April 2000 and another advisory meeting is planned for May 2002. A significant number of Planning Group representatives attended the initial meeting in 2000 and are expected to also participate in the upcoming session. The success of this ongoing planning process is demonstrated by the scope of the special type 1 diabetes funding program. Each of nine NIH institutes and centers and the CDC have lead responsibility for at least one type 1 diabetes research initiative that has been supported by the special funds through Fiscal Year 2002; further, the majority of these initiatives represent collaborative efforts between multiple NIH components.

THURSDAY, MARCH 14, 2002.

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. RUTH L. KIRSCHSTEIN, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ANDREW VON ESCHENBACH, M.D., DIRECTOR, NATIONAL CANCER INSTITUTE
DR. ANTHONY FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
DR. ALLEN SPIEGEL, M.D., DIRECTOR, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
DR. RICHARD HODES, M.D., DIRECTOR, NATIONAL INSTITUTE ON AGING
DR. AUDREY PENN, M.D., ACTING DIRECTOR, NATIONAL INSTITUTE ON NEUROLOGICAL DISORDERS AND STROKE
SUSAN QUANTIUS, ASSOCIATE DIRECTOR FOR BUDGET
KERRY WEEMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DHHS

Mr. REGULA. We will get started here. Thursday is going home day for members, so we have to get moving or we will lose them. Members commute, many, many even to California every week. I don't know how they handle the time change but they do. I would judge that probably two-thirds of the body pretty much commutes regularly. I haven't spent a week in here for years and haven't missed it either.

We are happy to welcome you back, Dr. Kirschstein. I met your nice husband. Together, you two have been a wonderful asset to this Nation. We appreciate what you mean to him. You will leave a legacy that will go far beyond your life or mine. Not everyone has that kind of privilege in this Nation, to leave something of lasting value that helps people for long term benefits.

Thank you all for coming. Dr. Kirschstein, you will make a brief statement for us and then introduce the members of your panel for their statements. We will be pleased to hear from you.

OPENING REMARKS

Dr. KIRSCHSTEIN. Thank you, Mr. Chairman.

Indeed, I do feel privileged to have served this country.

The Institute and Center directors of the individual units collectively constitute the National Institutes of Health and are pleased to have the opportunity over the next month or so to expand on these activities beyond the overview that you received yesterday. This will be accomplished through a series of panel discussions. Although each panel will only have a small number of participants, the area that will be covered at each session is of interest to, within the missions of, and broadly supported by all the Institutes and centers.

The clinical research advances listed in my opening statement are but a few selected to be representative of and to frame the theme for today's hearing, "From Bench to Bedside and Beyond." Such translational research illustrates progress from a basic discovery, usually at the laboratory level but not necessarily, to the patient's bedside and indeed in some areas beyond to the public as a whole.

As I said, I have provided in the written statement, several examples of that. My colleagues will now each present a small opening statement, I will introduce.

GENESIS OF THE NATIONAL INSTITUTES OF HEALTH

Mr. REGULA. When was the NIH started?

Dr. KIRSCHSTEIN. 1887.

Mr. REGULA. What was the genesis of it? I know CDC was a result of the Civil War. How did it come about?

Dr. KIRSCHSTEIN. The genesis of the National Institutes of Health was that in that period of time, post-Civil War, there was a great influx of immigrants to the United States, there was also a great deal of trade being carried on by our Merchant Seaman Service, both across the Pacific and from Asia and in the East Coast from Europe.

The people who took care of the merchant seamen when they were ill were in the commissioned corps of the United States Public Health Service, one of the uniformed services. Those merchant seamen were bringing into this country, as were the immigrants, large numbers of very, very serious infectious diseases, cholera, plague, smallpox, tuberculosis also malaria but it came another way. There was deep concern that we in this country had very little research going on. It was decided that a physician at the United States Marine Hospital on Staten Island would be sent to Europe to study in the great European laboratories of Koch and Pasteur to become a researcher able to handle that.

He came back after a year or so and established a one-room laboratory on the top floor of that hospital that was called the Laboratory of Hygiene.

Mr. REGULA. This was in New York?

Dr. KIRSCHSTEIN. In New York on Staten Island.

Early in the 1900s, that was expanded and the group moved to Washington, downtown, to the Butler Building I believe it was called. At that point, it became known as the National Institute of Health, singular, indeed continuing to study the scourges of the day that were killing vast numbers of people. The headline in the New York Times almost every day was "New Epidemic Hitting," yellow fever or something of the sort.

Then in 1937, a group of researchers and physicians at Harvard decided that the United States Government needed a cancer program. They wrote the President and a separate laboratory was set up at Harvard that became the National Cancer Institute, moved down and joined the single Institute which was the Hygienic Institute or the Microbiology Institute, the Institute that Dr. Fauci is now director of, and then new institutes were formed. The next one was the Heart Institute, then Mental Health and then Neurology and collectively then the name was changed to the National Insti-

tutes, plural, of Health. It moved out to the Bethesda campus in 1940.

Mr. REGULA. So there is no single founder in a sense?

Dr. KIRSCHSTEIN. The public founded, the Congress founded the National Institutes of Health.

Mr. REGULA. What a wonderful legacy that the people at that time had the vision to do this. I guess it is our responsibility to carry on.

OPENING REMARKS

Dr. KIRSCHSTEIN. Yes, sir.

The panel members will now present. Dr. Andrew von Eschenbach, the newly appointed Director of the National Cancer Institute, will present his statement, followed by Dr. Anthony Fauci, the Director of the National Institute of Allergy and Infectious Diseases; then Dr. Allen Spiegel, Director of the National Institute of Diabetes and Digestive and Kidney Diseases who will discuss primarily diabetes. Dr. Fauci will discuss primarily vaccines. Then we will have Dr. Richard Hodes, Director of the National Institute on Aging who will discuss primarily Alzheimer's Disease; and Dr. Audrey Penn, Acting Director of the National Institute of Neurological Disorders and Stroke will discuss primarily Parkinson's Disease.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Statement of the Director, Dr. Ruth L. Kirschstein,
to the House Appropriations Subcommittee on Labor-HHS-Education
March 14, 2002

on From Bench to Bedside and Beyond
accompanied by

Dr. Andrew von Eschenbach, Director, National Cancer Institute.
Dr. Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases
Dr. Allen Spiegel, Director, National Institute of Diabetes and Digestive and Kidney Diseases
Dr. Richard Hodes, Director, National Institute on Aging
Dr. Audrey Penn, Acting Director, National Institute on Neurological Disorders and Stroke
Ms. Susan Quantius, Associate Director for Budget
Mr. Kerry Weems, Deputy Assistant Secretary for Budget, DHHS

OPENING STATEMENT OF DR. RUTH L. KIRSCHSTEIN
PANEL – FROM BENCH TO BEDSIDE AND BEYOND
MARCH 14, 2002

Mr. Chairman, Members of the Committee:

The Institute and Center Directors of the individual units that collectively constitute the National Institutes of Health (NIH) are pleased to have the opportunities over the next month or so to expand on the activities of NIH beyond the overview you received yesterday. This will be accomplished through a series of panel discussions.

Although each panel will have only a small number of participants, the area that will be covered at each session is of interest to, within the missions of, and broadly supported by, all of the Institutes and Centers.

The clinical research advances listed below are but a few selected to be representative and to frame the theme for today's hearing: From Bench to Bedside and Beyond. Such translational research illustrates progress from a basic discovery, usually in the laboratory, to the patient's bedside and, indeed, in some areas, beyond, to the public as a whole.

Below are important examples of such clinical advances, which are but a few of the many that could be cited.

CANCER

Over the past 30 years, our nation's stable investment in cancer research has yielded significant dividends for patients and their families. A remarkable example is the development of Gleevec. Gleevec represents a whole new class of cancer drugs that are designed, targeting a complex of molecules, to block the growth of cancer cells while avoiding serious damage to healthy cells. Gleevec showed dramatic results in early clinical studies and was swiftly approved by the Food and Drug Administration last year as an oral treatment for chronic myeloid leukemia, which usually strikes middle-aged or older people. The drug is now being evaluated in the treatment of ovarian cancer, certain types of brain cancer, as well as a very rare form of stomach cancer and prostate cancer.

The National Cancer Institute (NCI) has recently developed a noninvasive blood test for ovarian cancer, one of the deadliest cancers for women, in part due to lack of effective screening methods. The new computer-based test will move quickly into clinical trials in which it will be used to monitor recurrence in recently-treated ovarian cancer patients.

VACCINES

Vaccines in general are recognized as the best payback of research investment because of the immediate impact on lives saved and illnesses avoided, which can be measured in the millions worldwide. To bridge the gap from basic research to applied research, the National Institute of Allergy and Infectious Diseases has built a network of clinical trial centers for testing vaccines both in this country and around the world; this network has already yielded successful vaccines and will be used in our future efforts for AIDS, malaria, and tuberculosis.

Vaccine research and development is the classic prototype of moving the fruits of basic research to applied research. For example, sequencing the genomes of pathogens has led to the identification of new antigens that are being used in clinical trials in the development of vaccines. This is an arena in which NIH classically has been successful in partnering with industry.

One of the major defenses for the country against bioterrorism threats is vaccination. Counter bioterrorism activities include: the NIH dilutional study of smallpox vaccine, which has expanded our store of 15 million doses to a range of 75 million to 150 million doses; current projects aimed at developing a new and improved anthrax vaccine; an Ebola vaccine that has been highly successful in an animal model and will enter clinical trials this year.

DIABETES

Type 1 Diabetes: Fundamental studies of the immune system and how it can cause the rejection of transplanted tissues and organs have led to the development of less toxic and more easily administered regimens and to new approaches to promote the immune system's "tolerance" and acceptance of grafted tissue. The goal of these new methods of immune tolerance is to eliminate the need for chronic immunosuppressive drug therapy in transplant recipients. Immune tolerance methods are now being actively tested in research studies in which type 1 diabetes patients are receiving transplants of insulin-producing islet cells and patients with irreversible kidney failure are receiving donor kidneys.

Type 2 Diabetes: Impressive results from a major, multi-center clinical trial, the Diabetes Prevention Program (DPP), demonstrate that modest improvements in diet and exercise can prevent or delay the onset of type 2 diabetes in at-risk individuals. These lifestyle changes reduced the risk of developing type 2 diabetes by 58 percent in a study population that reflected the diversity of the American public by age and by ethnic/racial groups. It is now imperative to translate these striking results to lifestyle changes of the 20 million Americans who are at high risk for type 2 diabetes due to their impaired glucose tolerance. To this end, researchers are seeking cost-effective means of targeting successful implementation of these prevention strategies to those who can most benefit from them, including high-risk minority groups who represented

45 percent of the study participants. Translation efforts will also target children and adolescents, with the goal of preventing or reducing obesity and its metabolic effects, including type 2 diabetes, am emerging problem in children.

ALZHEIMER'S DISEASE (AD)

The most common cause of dementia among people 65 and older, currently affects as many as 4 million Americans and their families. Basic research has identified important genetic, molecular, and cellular determinants of AD's underlying causes. We now understand how certain genes contribute to the development of amyloid plaque in the brain and how the plaque may contribute to the development of Alzheimer's Disease. Animal studies are helping us develop new treatments and preventive interventions, including drugs that block production of the amyloid and ways to remove it from the brain. Increasingly sophisticated neuro-imaging techniques hold promise of earlier and more accurate diagnosis of AD, improving the ability to predict its progression, as well as identifying persons at risk.

PARKINSON'S DISEASE

Drug Therapy: the use of the drug L-dopa, still the mainstay of Parkinson's therapy, is linked to many of the most fundamental studies in 20th century neuroscience. Basic studies revealed that the chemical dopamine is a neurotransmitter (sending signals to and from nerve cells) and led to the finding that in Parkinson's disease, it is the dopamine nerve cells that degenerate. This, in turn, led to a realization that the chemical L-dopa, the natural precursor of dopamine, might be used to treat Parkinson's disease. Studies showed that, indeed, L-dopa has a dramatic effect on the symptoms of the disease.

Surgical Interventions: The control of movement by the dopamine neurons laid the groundwork for surgical approaches and deep brain stimulation (DBS) in treating Parkinson's disease. DBS dramatically improves symptoms in some but not all patients. Surgeons rely on modern techniques to monitor electrical activity of nerve cells to locate precisely the optimal areas for stimulation.

Genetics: Astute clinicians long ago noticed that Parkinson's disease sometimes seems to run in families. Collaboration between clinicians studying Parkinson's families and molecular biologists, expert in finding genes, identified a gene defect that can cause the disease. Subsequent study showed that the defective protein, called synuclein, is found in the abnormal clumps in the brain called Lewy Bodies that neuropathologists had long ago identified as a hallmark of Parkinson's disease.

Cell and Tissue Transplantation Therapies: Decades of animal studies in both rats and non-human primates demonstrated the potential of neural tissue transplants in improving the functioning of Parkinson's disease patients. The mixed results of a recent clinical trial in terms of benefits and side effects, as well as the drawbacks of using tissue containing other than the desired dopamine neurons, led scientists back to

the laboratory and the study of methodologies to generate a safe supply of dopamine-producing neurons.

The panel members are:
Dr. Andrew von Eschenbach, the newly-appointed Director, National Cancer Institute.
Dr. Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases, who will discuss vaccines.
Dr. Allen Spiegel, Director, National Institute of Diabetes and Digestive and Kidney Diseases, who will discuss diabetes.
Dr. Richard Hodes, Director, National Institute on Aging, who will discuss Alzheimer's disease.
Dr. Audrey Penn, Acting Director, National Institute of Neurological Disorders and Stroke, who will discuss Parkinson's disease.

Dr. VON ESCHENBACH. Thank you.

Mr. Chairman and members of the subcommittee, I am Dr. Andrew von Eschenbach, Director, National Cancer Institute.

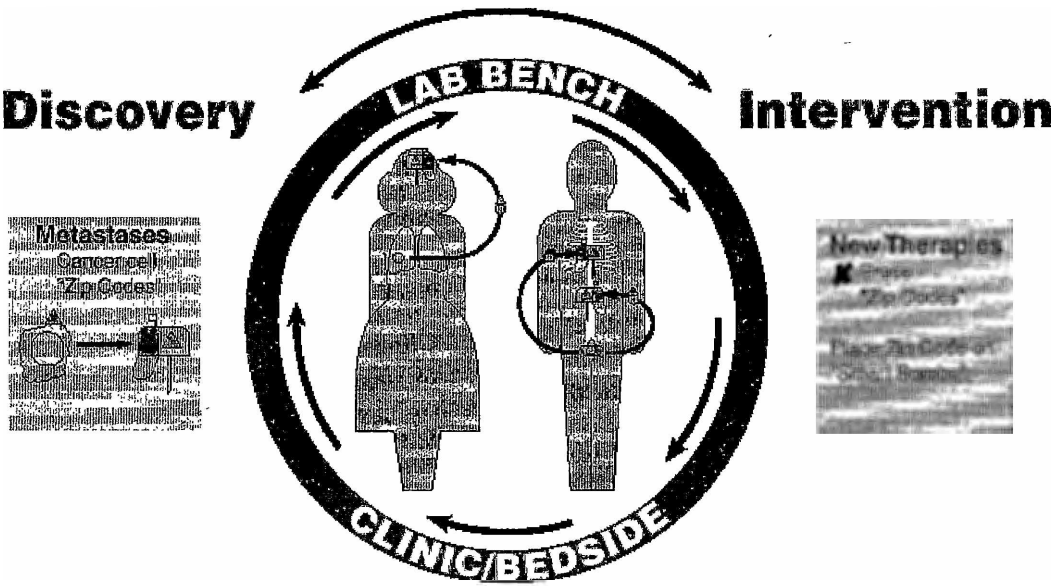
If I can begin with a small editorial comment, I want to thank you for your kindness and graciousness in recognizing Dr. Kirschstein yesterday morning for her 46 years of service to this country and to her husband, Dr. Rabson this morning for his 46 years of service to the National Cancer Institute. He was the Acting Director before I arrived. I can assure you that if you see how hard they both work, you can actually double those years in contribution.

I am very pleased for the first time to join my distinguished colleagues from NIH to discuss translational research and other activities supported by the NCI. The budget increases you have made possible over the past several years have allowed NCI to pursue an aggressive path of discovery in cancer research. While our journey is far from over, we continue to see promising results from these efforts. The latest statistics from our soon-to-be-released report to the Nation show that overall cancer mortality continues to decline. During the period 1990 to 1999, cancer death rates decreased by almost 6 percent, approximately 134,000 lives saved over that period.

The mysteries of cancer are yielding ground to our relentless and substantial commitment to research and the knowledge we gain in the laboratory is being translated into new interventions in the clinic to prevent and treat this disease. This is bench to bedside. While there are many chapters being written in this story, I would like to focus on one of the most recent advances that is represented on this poster.

[The information follows:]

Translational Research



CANCER METASTASIS

How cancer cells metastasize or spread to other parts of the body and kill and what we are going to do to stop this process is the focus of the poster. For decades in the clinic, physicians have recognized that cancer cells from certain organs have a characteristic propensity to spread to specific parts of the body. For example, lung cancers typically spread to the brain; prostate and breast cancers preferentially metastasize to bones. The question has been why. How do cancer cells know where to go?

Mr. REGULA. If you put a cancer cell on a slide and another cell, what would be the difference?

Dr. VON ESCHENBACH. The cancer cell would be abnormal both in its shape and its configuration and would have an abnormal appearance that a pathologist could recognize as being distinctly different from the normal.

Mr. REGULA. Do you know what makes that happen?

Dr. VON ESCHENBACH. We are beginning to understand that process at the genetic level. We know that there are certain genes that are abnormal that result in abnormal proteins that alter the structure and the function of that cancer cell such that it behaves in a malignant fashion.

Mr. REGULA. Does a cancer cell start out as a good cell?

Dr. VON ESCHENBACH. There are cells that start out as good cells that are then subsequently altered or damaged by a variety of mechanisms that then give rise to this malignant cascade of abnormal cells.

Mr. REGULA. Do we all have some cancer cells in our bodies?

Dr. VON ESCHENBACH. It is understood that at some point in time in our lives all of our cells are damaged to the extent that they could become cancer but our bodies have ways of repairing that damage. Ultimately, in one of two men and one of three women in this country, that process will emerge to an actual cancer. So it threatens all of us.

Mr. REGULA. So your mission is to try to alter the cancer cell so it doesn't misbehave or to keep it from happening?

Dr. VON ESCHENBACH. Both, sir. In the past, our strategy had been to just hopefully find the cancer and destroy it. Now, today, with this research, we are able to hopefully find it, alter it and change its behavior, control it and even prevent it.

Mr. REGULA. So the new therapy is not to excise it but to control it?

Dr. VON ESCHENBACH. That is correct, to complement what we have done before by also being able to control cancer much like we can control other diseases like high blood pressure. We may not be able to cure it but if we can control it and keep it from killing or destroying someone's life and creating the pain and suffering, then we will have succeeded.

Mr. REGULA. The killing mechanism is that it crowds out, it grows rapidly and crowds out healthy tissue?

Dr. VON ESCHENBACH. That is one of the processes. In fact, the reason to use this particular example of metastasis is that metastasis that spreads to other parts of the body is usually associated with the lethal or killing form of cancer. If we can prevent spread

and metastasis, we may be able to stop the killing type of cancer that we encounter.

ZIP CODES

Mr. REGULA. Thank you. I am sorry to interrupt.

Dr. VON ESCHENBACH. Not at all. So in this attack on metastasis and understanding how and why these cancer cells spread to other parts of the body, we have taken that question from the clinic to the laboratory to explore. NCI funded researchers have now determined that there are unique proteins on the surface of the cancer cell and that these proteins act like zip codes. When the cancer cell gets into the bloodstream, these zip codes on the cell can direct it only to specific locations or mailboxes that have that address.

For example, within the bone, there are unique receptors for the zip code protein that is present on prostate cancer cells. Your research dollars have made these discoveries possible and future research dollars will support taking this knowledge from the laboratory back to the clinic by developing interventions that could erase the zip codes so that the cancer cell can never get to its destination or use the zip codes to address cancer killing smart bomb therapies that will go only to the tumor site.

These and many other exciting chapters in our story of scientific discovery are yet to be fully realized but are well on the way to being written. Mr. Chairman and members of the subcommittee, the goal of the National Cancer Institute is to wisely spend the dollars proposed in the President's budget for further scientific discovery such as these and then to translate that discovery into methods that will detect, treat and prevent cancer. Only when we have saved lives and restored the quality of life in the one of two men and one of three women who will develop cancer, will our mission be complete.

I thank you for the opportunity to testify about this important aspect of cancer research and I will be pleased to answer your questions.

Mr. REGULA. Thank you.

Dr. KIRSCHSTEIN. Dr. Fauci.

CONCEPTION AND DEVELOPMENT OF VACCINES

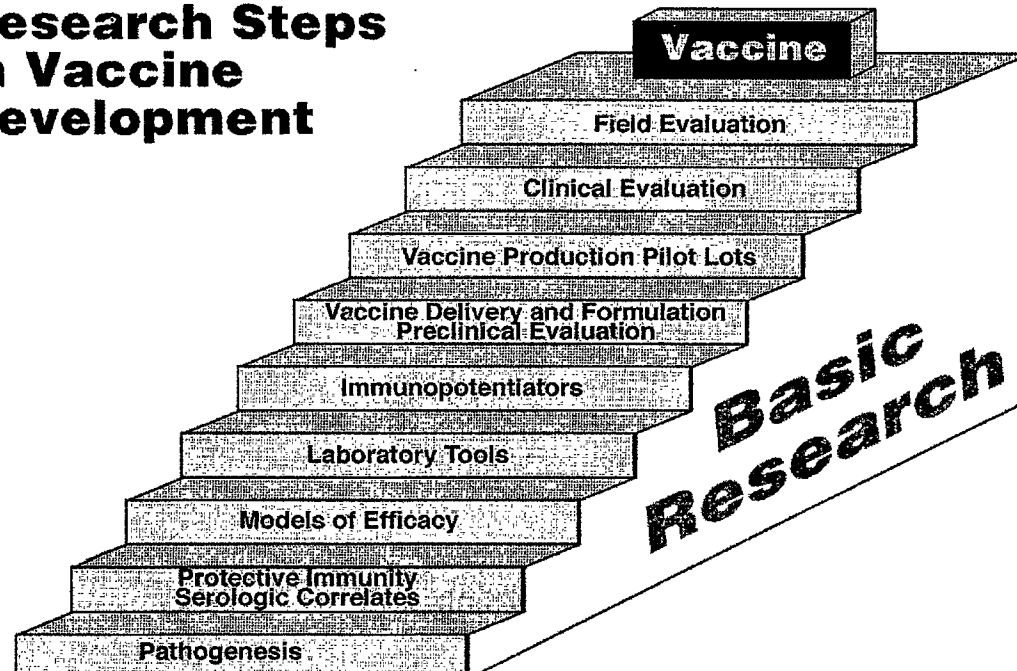
Dr. FAUCI. Mr. Chairman, Mr. Miller and Mr. Peterson, it is a pleasure to be here with you again.

In the two to three minutes allocated to me, I am going to talk a bit about the conception and development of vaccines and the role of the NIH in vaccine development, which really stands as one of the important prototypes of the true bench-to-bedside concept we are discussing here this morning.

I have outlined on this slide, the fundamental basis for the development of vaccines which is really anchored on the concept of basic research for which the NIH takes a major responsibility in the collaborative effort between industry, academia and the NIH.

[The information follows:]

Research Steps in Vaccine Development



If one looks at the steps, I have done this schematically in a metaphorical way here, looking at the development ultimately of a vaccine, we learn about the pathogenesis of microbes, look at ways to enhance the immune response, there is clinical evaluation and ultimately one develops a vaccine.

If you were to pick out what the top economically important components of what the NIH does in cost benefit in health to the Nation, without a doubt vaccines has to be on everyone's short list in that regard. Let me give you some very brief examples.

These are just four representative examples of vaccines that have been developed at the NIH together with our industrial partners, concepts that were formulated either at the NIH or by NIH-funded grantees and contractors. On the righthand side of the slide are the potential lives saved each year from the proper execution of these vaccine programs.

[The information follows:]

Recently Developed Vaccines and Their Life-Saving Potential

	Worldwide Deaths/Year
■ Hepatitis B	>1,000,000
■ *H. influenzae* type b	700,000
■ Acellular pertussis	350,000
■ Pneumococcal conjugate	1,200,000

NIH Vaccine Research: Important Priorities

- AIDS
- Malaria
- Tuberculosis
- Bioterrorism
  - Smallpox
  - Anthrax
  - Ebola

As you can see, four key examples—Hepatitis B, Haemophilus influenzae type b, acellular pertussis, and pneumococcal conjugate. If I take this one, Haemophilus influenzae type b, which was developed in collaboration with the Child Health Institute, in just a few short years, we have taken a disease that had been the primary cause of microbial-induced deafness and mental retardation in children in the United States and worldwide, and essentially are on the brink now of eliminating that infection in much the same way as we have eliminated smallpox and are well on our way to eliminating polio, both of which were done through vaccinology.

This last poster tells us about the challenges for the future because although the victories have been most extraordinary over the past several decades, we still have a lot to do. These are some of the challenges that we will be facing and hopefully I will have the opportunity to discuss before this committee in years to come. That is, the challenges for an AIDS, malaria and tuberculosis vaccine, the three great killers in developing nations, and the threat we find ourselves in unfortunately in our Nation today, the threat of bioterrorism. Vaccines will be one of the major tools, particularly those new and improved vaccines against smallpox, anthrax and other frightening diseases such as ebola. These are going to be the goals and the milestones for which we will aim over the next few years.

As I mentioned, hopefully we will have some important results for you over the next few years.

Thank you very much for giving me this opportunity and I would be happy to answer any questions.

DIABETES RESEARCH

Mr. REGULA. Thank you. Dr. Allen Spiegel.

Dr. SPIEGEL. Thank you, Mr. Chairman.

The research mission of the National Institute of Diabetes and Digestive and Kidney Diseases encompasses a wide array of chronic disabling diseases. Today, I have been asked to focus my remarks on diabetes, but I would be pleased to take questions on all of our programs.

Diabetes research is an excellent example of how fundamental discoveries in the laboratory are translated into clinical research, and then beyond, to improved public health.

The poster illustrates what research has taught us about the stages in the natural history of diabetes. People with diabetes progress from being able to maintain a normal blood sugar or glucose level to a pre-diabetic state termed IGT, then to overt diabetes. In both major forms of the disease, type 1 and type 2 diabetes, poor control of blood sugar leads to abnormal blood vessels in the eyes, kidneys and nerves. If unchecked, these blood vessel complications of diabetes can progress to blindness, amputations, and kidney failure, and to death most often from heart disease.

NIH supported research has shown that prevention is possible at each stage of the disease: preventing disability and death from the complications, preventing the complications themselves, and perhaps most importantly from a public health point of view, even preventing the development of diabetes. Given time constraints, I will just give a few examples of how research at NIH has made prevention possible.

Basic research has shown that elevated blood glucose activates a protein termed PKC, leading to the diabetic complications. Specific inhibitors of PKC were shown to block development of the complications in animal models of diabetes. Currently, these inhibitors are being tested to prevent diabetic complications in humans in advanced clinical trials.

Type 1 diabetes affects nearly a million Americans, mostly children. Fundamental research has illuminated how a malfunctioning immune system destroys the insulin-producing beta cells of the pancreas causing this disease. This knowledge has led to several approaches for re-educating the immune system, with the goal of preventing type 1 diabetes in those at risk. These approaches are being rapidly tested in NIH-supported clinical trials.

In parallel, we have a vigorous program aimed at more effective treatment, and indeed, complete cure of type 1 diabetes in those already affected. New hope emanates from successful preliminary studies in which transplantation of beta cell clusters known as islets has restored natural insulin-producing capacity to type 1 diabetes patients.

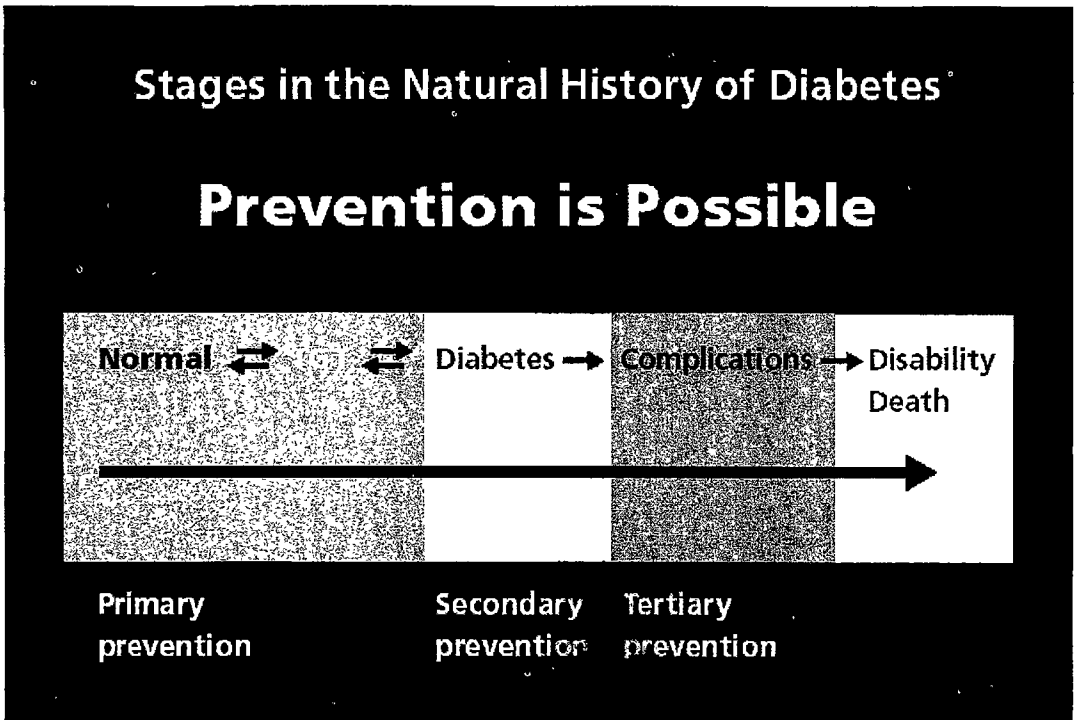
Turning to type 2 diabetes, which affects approximately 15 million Americans, we see a disease that is reaching epidemic proportions in the U.S.—rising in incidence by nearly 50 percent just from 1990 to 2000. Basic research has identified new targets for more effective treatment of type 2 diabetes.

Clinical trials have shown that, with effective treatment, the complications of both forms of diabetes can be prevented.

NIH-supported research also shows that primary prevention of type 2 diabetes, a critical public health goal, is possible. Last August, we announced impressive results from a major multicenter clinical trial, the Diabetes Prevention Program or DPP. Modest improvements in diet and exercise decreased the development of type 2 diabetes by a remarkable 58 percent in high-risk individuals in the trial. Now, we are working on methods for cost-effective translation of the DPP results to the estimated 20 million Americans with IGT who are at high-risk for type 2 diabetes. Prevention efforts offer our best hope of stemming the tide of this diabetes epidemic and averting the huge burden of suffering and health care costs.

Thank you for your attention.

[The information follows:]


Stages in the Natural History of Diabetes
Prevention is Possible
Normal
Diabetes
Complications
Disability
Death
Primary prevention
Secondary prevention
Tertiary prevention

Dr. KIRSCHSTEIN. As we turn to the members sitting to the right, I also would like to introduce Mr. Kerry Weems who is from the Department.

ALZHEIMER'S DISEASE

Mr. REGULA. We are beginning to get to know him well.

Dr. KIRSCHSTEIN. Dr. Hodes from the Aging Institute.

Dr. HODES. Thank you. It is a privilege to be here testifying before the subcommittee again.

The National Institute on Aging has as its mandate efforts to improve the quality of life for older men and women through addressing a variety of conditions.

Mr. REGULA. What is the definition of older?

Dr. HODES. It is generally 10 to 20 years older than oneself. [Laughter.]

Mr. REGULA. Touche.

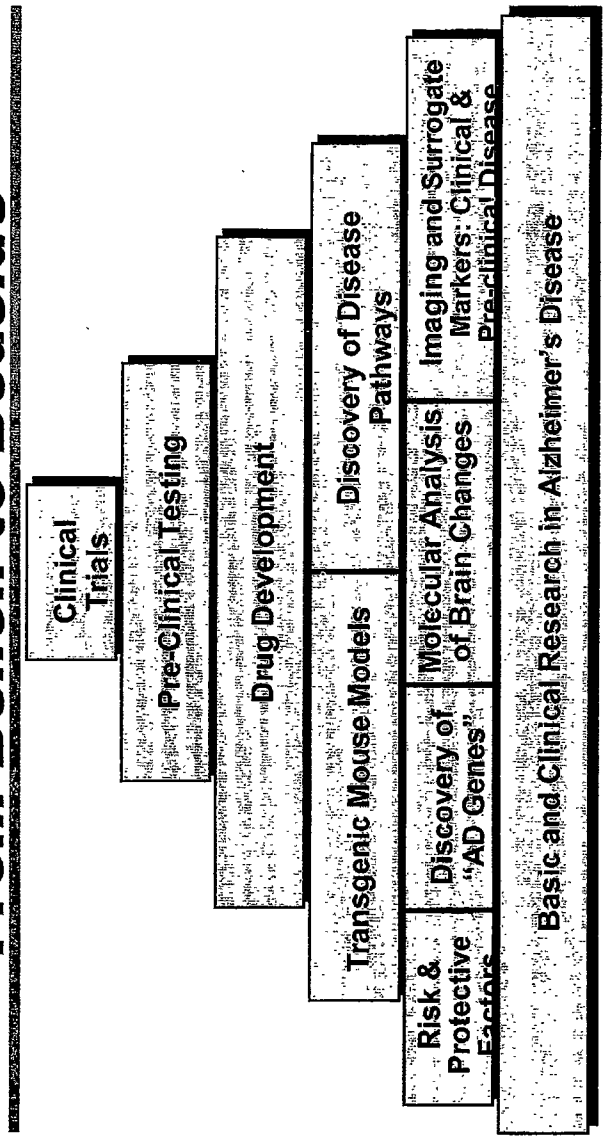
Dr. HODES. Among those many conditions, it is my opportunity this morning to talk about Alzheimer's disease, a major cause of dementia that affects some 4 million Americans currently, with devastating effects on those affected, as well as loved ones, caretakers, and ultimately society. This in the context of an aging American demography, projects a risk of several times this number of Americans will have Alzheimers Disease in decades to come.

It is hard now to remember that as recently as 30 years ago there was really not an appreciation of the fact that Alzheimer's existed as a discrete condition. It is on that background, that it is a real pleasure to talk about the progress that has been made and the experimental laboratory bench to bedside approach that has been taken to understanding and approaching this disease.

Basic research in the area of epidemiology has identified a number of risk factors, meaning factors that put people at high risk for developing Alzheimer's disease. Among these is the identification of several genes which can when mutated, actually cause the disease. This has led to an understanding of the biochemistry, the cellular events that underlie the Alzheimer's disease process and has allowed for the first time in recent years the development of animal models so that one is now capable of taking the genes that can cause Alzheimer's disease in humans, incorporating them into mice and seeing in those mice some of the brain lesions characteristic of Alzheimer's disease, as well as some of the memory and learning deficits.

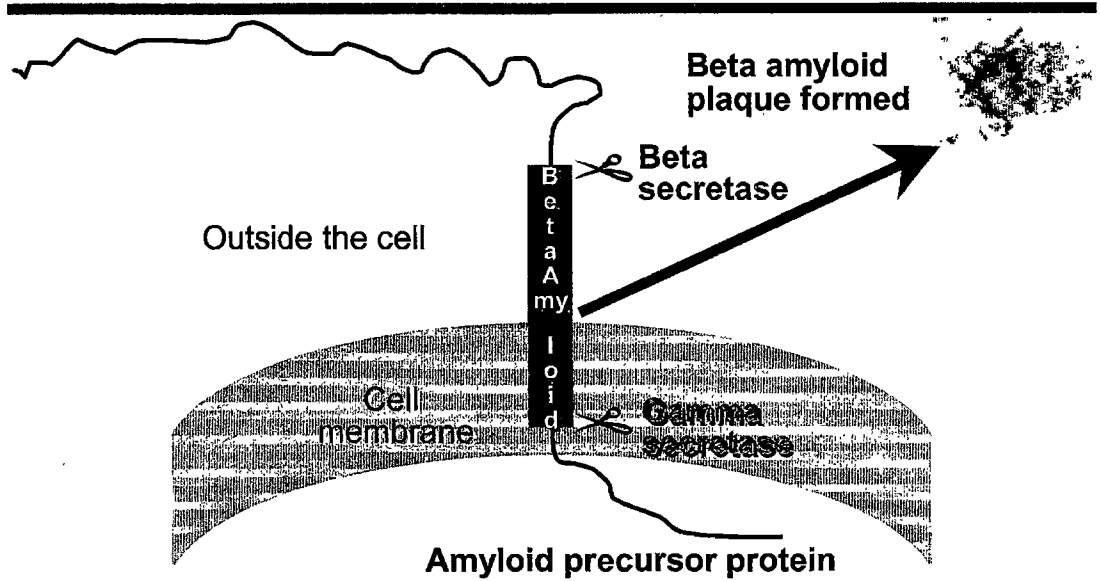
For the first time as illustrated here, this means one can now take drug development through stages that involve animal models, preclinical research looking for those interventions which are most promising, and then taking them on to clinical trials.

[The information follows:]


From Bench to Bedside
Chart 1
Clinical Trials
Pre-Clinical Testing
Drug Development
Discovery of Disease Pathways
Transgenic Mouse Models
Molecular Analysis of Brain Changes
Imaging and Surrogate Markers: Clinical & Pre-clinical Disease
Risk & Protective Factors
Discovery of "AD Genes"
Basic and Clinical Research in Alzheimer's Disease

Production of Amyloid Plaques

Chart 2



PREVENTION OF ALZHEIMER'S DISEASE

There is as yet no effective prevention or curative treatment for Alzheimer's disease, but again through the budget that has been made available to NIH and the National Institute on Aging over the past years, we have been able to take these dramatic advances in basic science and translate them into current clinical trials numbering some 18,007 of which are large scale prevention trials.

Prevention trials in the case of Alzheimer's disease are particularly important since it is far more likely that we will be able to succeed in preventing damage than to reverse cell death and dysfunction of the brain once it has occurred.

The second poster illustrates an example of the specificity with which we now understand some of the processes that underlie Alzheimer's disease. It is an illustration on the top right of the beta amyloid plaque. This is the plaque lesion that is seen in the brains of individuals with Alzheimer's disease. As a result of research over the past several years, we have learned that plaques consist of material called amyloid peptide which in turn is the product of the beta amyloid precursor, that red bar you see in the surface of all normal cells. We now understand that to translate that normal protein into the plaque typical of Alzheimer's disease requires the activity of a number of enzymes, beta and gamma secratase. It is only when these scissors work together to cut the normal protein in such a way that they produce this amyloid peptide that causes plaques and may lead to memory loss in animal models and in at least some human genetically determined cases of Alzheimer's disease.

Armed with such information, we are now capable for the first time of designing interventions to remove or prevent the formation of amyloid plaques, to interfere with the enzymes that cause the disease. We face a situation in which although the cure is not yet in hand, scientists, investigators and all of us, I think, have reason to be hopeful this improved understanding will translate to effective treatment and ultimately prevention.

Mr. REGULA. Where they could take the cell out and take out the gene that creates Alzheimer's and then put it back in? There was a story recently.

Dr. HODES. Yes. About 10 to 15 percent of Alzheimer's disease is early onset, familial, genetic. In those cases, there is a mutation in a single gene which causes Alzheimer's disease. It is inherited so one can predict by looking at the cells passed on from mother or father to offspring whether that individual will be at risk for Alzheimer's or not.

The article referred to the ability to look at a fertilized egg from a mother or father who carries the disease and ask whether a given egg is one of the 50 percent that will carry that Alzheimer's gene or is one of the 50 percent that will not. Clearly the ethical and societal implications of this are enormous, but in terms of the ability to translate science to knowledge, it is possible by that sort of test to identify whether in that instance a mother or father has or has not passed on the gene for Alzheimer's disease to a child.

This is now possible in that minority, 10 to 15 percent, of Alzheimer's cases that are of known genetic origin, but is not true of the bulk of late onset Alzheimer disease.

I thank you for the opportunity to present these examples and look forward to a chance to discuss with you further any issues of interest to the committee.

Dr. KIRSCHSTEIN. Dr. Audrey Penn, the Acting Director of the Neurological Disorders and Stroke Institute.

Dr. PENN. Good morning.

PARKINSON'S DISEASE

Important developments from several types of basic neuroscience are coming together to reveal the causes of Parkinson's disease and to identify treatments.

Parkinson's is a debilitating neurodegenerative disease which results from loss of dopamine nerve cells in specific clusters deep in the brain. Thirty years ago, scientists at the bench found the signaling molecule dopamine was concentrated in these basal ganglia. You can see the white region on the left, and what is lost in Parkinson's brains as you see on the right.

[The information follows:]

SPECT DOPASCAN

Healthy

Parkinson's

This resulted in the first effective medical therapy, L-dopa, which replaces the dopamine. Neurosurgeons had for years tried unsuccessfully to control the abnormal movements of Parkinson's by making small wounds or lesions in the main motor pathways from the brain to the spinal cord.

In 1954, during such a surgery, the inadvertent interruption of a small artery which supplied the key basal ganglia, strikingly improved a Parkinson's patient, and surgery aimed at the basal ganglia was a major therapeutic strategy until the advent of L-dopa, when it was abandoned. However, we all know that L-dopa is not a perfect therapy.

Years of neurophysiological investigations of control of movements using microelectrodes to measure the electrical activity emanating from the cells in the basal ganglia, the large complex there, have now permitted specific targeting of surgery in Parkinson's. Even more importantly, simply stimulating key targets, a small area no bigger than a green olive deep in the brain, is really strikingly improving patients.

[The information follows:]

PROBE PLACEMENT
IN DBS
STIMULATOR
CAUDATE
NUCLEUS
PUTAMEN
GLOBUS PALLIDUS
STN
LD
Pul
VA
VL
VPM
CM
SC
IC
PPN
ZI
H
SN
RN
SI
AC
OT

Deep brain stimulation is providing benefit while extraordinary investigative efforts are providing new information as to the mechanisms of this disease.

The availability of families with multiple members affected with Parkinson's allowed identification of defective genes, and then the defective proteins, now known to be important to mechanisms of degeneration, since they are involved in the production of the characteristic pathology, in this case Lewy Bodies. In turn, understanding the cellular roles of these proteins suggests new therapies. Detective work at the bench showed the "frozen" heroin addicts recognized to have severe Parkinsonian rigidity had been damaged by a byproduct of heroin called MPTP, and now we expose animal models to this MPTP and we have great models to examine mechanisms, and to test our new therapies.

Our investigators are very enthusiastic about all of this new information and are working together ensuring resources to pursue all clues. Some of this cooperation has developed as the scientists of the 11 Udall Centers meet regularly and focus on Parkinson's disease. The scientists agree that the rate of progress is impressive.

All current therapeutic strategies arose from fundamental bench research, which was furthered by cross fertilization from applied research and other neurodegenerative diseases. At multiple stages, clinical studies have generated, and continue to generate, new questions for the basic scientist to address. As the interrelationships between the likely mechanisms of damage become clearer, we come even closer not only to therapies, but also to prevention.

I would be pleased to answer any questions.

Mr. REGULA. I want to say at the outset, I admire all of you and the work you do. I don't think people fully appreciate how important your work is to their well being. We just sort of take these things for granted but all of you do the work of the Lord.

Mr. Miller.

CANCER RESEARCH

Mr. MILLER. Dr. von Eschenbach, congratulations on your appointment.

As the Chairman said, it is always an honor to have you all here. I always feel guilty that you only get two to three minutes to talk. I feel bad that we have so many conflicts of meetings at this time that we don't get a chance to be able to participate. I also feel at times that you are just so over our heads as lay people here.

You keep using John Porter's comment as the crown jewel and unfortunately not as many people realize what we have. I think it is unfortunate.

I remember at a county commission meeting in my hometown. My wife is very active in the library system and they were asking for more money for the library. The county commissioner asked the director of the library, have you read every book in the library and he said no. He said, well, why do you need more books. Sometimes politicians don't realize what we have. I think we need to do more to toot our own horn.

There was a story on television the other day about a big book store in Northern Virginia on Soviet studies that is going out of business, the largest one in the western world. They went bankrupt

and went out of business. All of us remember the Cold War and actually Russian studies, Soviet studies was a big issue at universities with big programs. Now there is not much interest in that, it has changed dramatically. Russian studies, the Russian language is no longer at the forefront of our interest because of the collapse of the Berlin Wall and what has happened since then.

Do you see those type breakthroughs that your successors will be like? Will you or your successors in 2012 be talking about the same things? How will it change and be different in 2012 or 2017? There is so much in the pipeline. You see a lot of the studies going on. Are you going to be out of business in 12 years?

Dr. VON ESCHENBACH. God, I hope so. I think your point is an important one. What I have seen is we are beginning to change our approach to cancer so that by understanding it at the biologic level, one, we will change it to a chronic disease that we can manage; two, hopefully completely eliminate it but much of the knowledge we gain could be then applied to many other diseases. So although we will go out of business, the yield will be more widely applicable.

For example, research done in cancer to understand how cancer cells induce the development of blood vessels to get food and oxygen, that research has led to treatments now being applied to problems like macular degeneration and diabetic retinopathy in the eye. We hope to put ourselves out of the cancer business but at the same time able to use the products and benefits of our research that will then benefit other diseases over time.

Mr. MILLER. Do you think you will be treating prostate cancer? I was told there was a chance anybody who was old enough would get prostate cancer. It is extremely slow growing so maybe you don't need to do much about it. Are we still going to be worrying about prostate cancer or breast cancer 12 years from now?

Dr. VON ESCHENBACH. I think both of them are particular examples of this new concept. With prostate cancer, we know many men develop prostate cancer, it remains relatively innocuous and they live their entire lives and die with it rather than from it.

On the other hand, there is a subset of men who have a very virulent form of the disease and prostate cancer is the second leading cause of death in men. So one of the purposes of this kind of research is to understand the difference between the two. Why are some prostate cancers innocuous, why are others virulent and more importantly, once we know that, can we change the virulent ones into the innocuous ones and then men can live perfectly normal, healthy lives with us controlling their cancer and not having to put them through the radical kinds of treatments that we have had to use to this point in time?

CONQUERING DISEASE

Dr. FAUCI. Speaking about going out of business, I remember in 1968 when I was driving down from my residency at the New York Hospital on my way to take an infectious disease fellowship at the NIH. At that time, literally as I was driving down the New Jersey Turnpike, there was an announcement that then Surgeon General William Stewart had announced that now with antibiotics and vaccines, the problems of the world with infectious diseases are over and we should be concentrating on chronic diseases.

When I got to the Baltimore Harbor Tunnel, I wanted to turn around and go back to New York because I didn't need to take an infectious diseases fellowship. As we know, since then, we have had the HIV epidemic, emerging and reemerging diseases and now we have the threat of bioterrorism.

From the standpoint of infectious diseases that delicate balance between microbes and the human host is one that we must continue to stay ahead of. That has to do with understanding the microbes better. What I foresee in years to come is having the sequences, the genomic sequences of essentially all of the pathogens and being able to identify targets for diagnostics, for therapeutics and for vaccines so that as new diseases emerge, the human species will in fact stay very much ahead of the curve as opposed to chasing epidemics.

I think we have a lot of work ahead of us but only by continuing the intensity of the research are we going to stay ahead of that curve.

There will be a never-ending interaction between microbes and the human species. I believe we will conquer HIV/AIDS with a vaccine and with even better therapies but other diseases will come along, the same way the flu pandemic came along in 1918 and wreaked such havoc on the population. I think it is naive to think that we are not going to see other microbes in the future do the same thing.

HIV VACCINES

Mr. REGULA. What is in the pipeline now at the different phases of testing for AIDS, for HIV?

Dr. FAUCI. Actually this has been a very important year with regard to the concepts of HIV vaccines. At the national conference in Seattle just last month, there were a couple of concepts, one that we are doing in collaboration with the Merck Company in a vaccine that incorporates putting together genes from different viruses so that you can vaccinate someone with an adenovirus which is a common virus that infects man but that has the genes of HIV inserted into the adenovirus so that it can act in a way that stimulates a very potent immune response.

We are going to be going into advanced phase studies in the next couple of years. We are already in Phase I studies. So the news is starting to look much better. We have been before this committee many years in the past talking about caution in thinking that we are going to win this war in the next year or so. It is going to be a long way but I am very optimistic about what has gone on over the past couple of years in the area of HIV vaccines.

HUMAN GENOME SEQUENCE

Dr. SPIEGEL. Your tremendous support has allowed us to obtain the "book" of the human genome sequence. This resource now is critical in terms of our being able to read and understand that sequence and apply that knowledge. One example from NIDDK is polycystic kidney disease (PDK), one of the most common genetic diseases, an important cause of end stage kidney failure, which costs $18 billion a year in this country. We now know the genes that cause this disease.

In the case of Crohn's disease, a severe inflammatory bowel disease, our investigators have just identified a gene in the last year that increases the risk for getting this disease by as much as 40-fold.

In type 1 diabetes, we know several of the genes that provide increased risk. Our investigators are working on taking that genetic knowledge and turning it into therapies and prevention. I believe that is what is in the pipeline. Continued investment will allow that knowledge to be applied in practical terms.

It isn't all the genes. If we come back to the type 2 diabetes example, it is critical that individuals who are susceptible learn what it is in the environment—the combinations of dietary changes and environmental changes in terms of exercise that can prevent the development of diabetes. The study I alluded to in my statement shows this can be done. It was done in 3,200 individuals of all races and ethnicities, 45 percent of whom were minority individuals.

TRANSLATING DISCOVERIES

Mr. PETERSON. I always find it stimulating to listen to you folks. I have a question. As the Congress and the Administration have made a push to fund research adequately and to give you the ability to move forward, do we have any operations that measures how these discoveries get implemented to the public. As I looked at your sign, it ought to say bench to prevent the need of a bed. I don't look forward to a treatment being bedridden.

You are coming up with wonderful new data and information and immunizations but at the same time, are we a healthier population in this country? The answer is no. There is a disconnect between what you are learning and what the American people are doing in their utilization of what you are learning. For some reason, this country is less healthy than it was five or ten years ago by personal choices and lack of things we could be doing to be healthy.

With all this great success, I am concerned that there is somehow a disconnect.

Dr. SPIEGEL. That is a tough question. I agree with you, but let me elaborate.

Let's come back to the type 1 diabetes, that affects about a million Americans, which used to be called the juvenile form. Just over the last two decades, the life expectancy of individuals with type 1 diabetes has gone up by between 10 to 15 years. That is a measurable, real, improved outcome. It is really because of advances in the therapy of those individuals that life expectancy has increased.

A clinical trial that was done at NIH, the Diabetes Control and Complications Trial, which ended in 1993 showed that tight control of blood sugar can prevent the blindness, kidney disease and amputations from this disease. This advance has led to a decline in blood sugar measured by the hemoglobin A1c test in type 1 diabetes patient. So there are positive performance measures.

However, you are absolutely right in terms of the role of environment in type 2 diabetes—the choices in terms of healthy lifestyle. This is in part why we need to decrease the time between a clinical trial result, like the one we announced in August, and how we translate that to the public.

We have science-based information on websites and in booklets that we distribute around the country through our National Diabetes Education Program. People can see if they are at risk for type 2 diabetes. They can self-identify whether they need to go in and be screened. It isn't futile; you can actually do something about it. We know individuals with type 2 diabetes have a fourfold increase of heart attacks. Women who are protected from heart attacks if they don't have diabetes lose that protection with diabetes. That is why we have a new National Diabetes Education Program, "ABCs" campaign. This campaign emphasizes controlling not only the blood sugar, but also blood pressure and cholesterol.

I totally agree with you that it is useless to just generate the knowledge. We and all the Institutes are committed to translating this knowledge. That is why our goal is "bench-to-bedside and beyond."

Dr. FAUCI. Let me give you a couple of very brief examples of why things are better off now. If you take a very important disease in the United States, HIV/AIDS, in which there are still 950,000 people infected, the deaths from HIV/AIDS over the last several years have decreased by 75 percent because of the bench-to-bedside development and conception of drugs, and the application and distribution of now very effective antiretroviral therapies. The deaths in 1996 were 50,000, in the year 2001 it was 13,000. That is with a constant infection rate. I believe that is a very good example.

Another example is the one I gave in the vaccine study, when you are at Haemophilus influenza b in which thousands of children each year became mentally retarded or deaf due to influenza b, but because of a bench-to-bedside approach of vaccine development and the execution of the vaccine trials, that disease has essentially disappeared from the United States.

Those are two examples of how things are being translated.

DISABILITY DECLINE

Dr. KIRSCHSTEIN. Dr. Hodes.

Dr. HODES. I would like to begin by stepping back to broad statistics. There has been concern as the nation and the world face an aging demography in its population that as we extended life we would see a population in which more and more older individuals survive but survive with great disability and where quality of life would be compromised.

In that respect, there has been some extremely heartening and positive data over the past years that have shown significant changes since 1982 when approximately 25 percent of older Americans, defined as age 65 and older, were disabled. Data through the present estimate have shown this disability rate to have decreased steadily over that interval to approximately 19.6 percent, a very substantial decrease in age-adjusted disability.

This means that there is no irrevocable destiny that as people grow old, they will be infirm and disabled. The causes that contribute to this are many. When one looks at factors that correlate with survival without disability, perhaps the best correlation is with education. Education is manifesting itself in many ways. It may involve some direct biological event such as the conditioning of the brain to prevent dementia. It may be that with education

one is better able to take advantage of medical and public health advances. There is no question it is among the best correlates or predictors of this decreasing disability.

In terms of specific examples of research that has been translated into practice, one that was alluded to by Dr. Spiegel was the area of hypertension. For a long time, people were accustomed to paying attention only to diastolic hypertension. Blood pressure is always expressed as a high number over low number. That low number, the diastolic blood pressure, is what we were traditionally taught was the most dangerous and needed to be controlled. Older people, as a population, statistically tend to increase their systolic blood pressure and this was most often ignored as just a side affect of aging to be accepted.

Over the past years in collaboration with the Heart, Lung and Blood Institute, the National Institute on Aging has been a part of a study which examined what could be accomplished by treating systolic hypertension in older people with a drug, a diuretic that costs literally pennies a day. The outcomes have been quite incredible.

This therapy has been successful in reducing the incidence of congestive heart failure years later by 50 percent. If one looks at those individuals who already have a history of cardiac disease, the likelihood of their developing congestive heart failure has been decreased by 80 percent.

So research has without question, led to interventions which are increasingly known to the public and to the medical care providing establishment, but to reemphasize what you have heard, a large part of the challenge that remains is implementing these, communicating to the public in an effective way, and finding ways to have as many people as possible take advantage of what can be offered as proof of research based investigation.

INFORMATION DISSEMINATION

Mr. PETERSON. I have an aunt and uncle who are 94 and 95. He is 94, still drives a car, does most everything. She is 95 and she still makes a mean apple pie. They have utilized everything that you people are doing. He was in the health care business. He ran Blue Cross of Illinois years ago, so they live healthy lifestyles. They exercise, eat their fruits and vegetables, do all the things right, but most Americans aren't doing that.

Those who are plugged in and are listening and paying attention to health are benefitting from what you are doing, but a large percentage of our population has disconnected that what they do has anything to do with how healthy they are going to be.

Dr. HODES. No question, and I think all of us realize part of the mission of NIH in addition to carrying out research is in the dissemination of information. Regarding the area you mentioned of exercise, for older people it wasn't so long ago that a doctor's advice was take it easy, you are old, don't hurt yourself. A large body of exercise intervention research has now indicated that for older people, strength training or aerobic training can have enormously positive effects.

In terms of communicating to the public, after the weight of these research accomplishments became overwhelming, NIA devel-

oped a publication, an exercise manual for older people. As evidence of the fact that there is a public willing to take advantage and listen, this exercise guide was made available free to the public, one copy at a time in response to requests. It has now been distributed to over 430,000 older Americans, and now accompanied by a video that is distributed for cost recovery. We hope this trend is going to increase. We are in the process now of studying the next important question. For those who have asked for the book, how many people are exercising and what will be the outcome in their overall health?

Dr. KIRSCHSTEIN. Dr. Penn.

Dr. PENN. One of our other major diseases has placed us right here and that is stroke. In stroke, we are really finding that we had better address prevention and intervention issues along with the research. They inform each other, as we said before but we are engaged, with the help of Madison Avenue pro bono and many of our voluntary organizations—actually have a memorandum of understanding with the American Heart Association and with the Heart, Lung and Blood Institute and with the Surgeon General—we are trying to get out there and instruct people on the signs of stroke and what they can do to prevent it.

As you might have heard, all the risk factors for diabetes and a lot of the risk factors for heart disease are right there for stroke. It is even more important, or just as important, in our minority populations who are, in many cases, having more strokes. We are trying to work on the elderly because the elderly have this propensity for abnormal heart rhythm where you throw pieces of clot into the brain.

We have found that neurologists can't disengage themselves from this. We have a lot of therapies—probably all of us should be taking one aspirin a day—and we had better get on with the implementation of what we have learned so far.

Dr. VON ESCHENBACH. One additional comment. I think your point is extremely well taken. One of the things we are paying a great deal of attention to at the National Cancer Institute is to do research on how to get the message across and why patients or people are not accepting the kind of healthy lifestyles we know would prevent or offset the kind of problems you alluded to.

Next year, we anticipate over $324 million of our budget will be directed just to health behavior research so we can break those barriers down, make certain that we are appropriately getting the kind of response from the American people that we need. That is particularly true in minority and underserved communities.

Mr. PETERSON. One of my suggestions would be to somehow engage the health care community. I visit 18 hospitals in my district. Obesity abounds in the hospitals. That is not a good example. I live across the street from a very busy family physician. The vast majority of the seniors that visit him, the major part of his patient base, are obese. It is the majority that come in there. I can't believe he is not talking about that because, I have one man that is 57 years old and I said does he talk to you about being obese and he said no.

If the health care community isn't going to tell the population they are dealing with about healthy lifestyles, who is going to?

Mr. REGULA. I think you have touched on a tough subject. When we finish with questions, I would like each of you to say how you disseminate the information you gained to 280 million Americans.

Ms. Pelosi.

Ms. PELOSI. Thank you. I appreciate the concern raised by Mr. Peterson and the response he received thus far. I look forward to further responses from our distinguished panel. It is a great day for us when you all come in. We are so proud of you and thank you for what you do.

I think another part of the problem is many Americans don't have access to health care and there is a disparity when we talk about the minority population and those with less education, and those who are economically disadvantaged. They simply are not in the loop, they don't even have a chance to talk to the doctor about obesity because they don't go to one.

I think we will be a healthier country and I appreciate your question, Mr. Peterson, that those who are in the loop are not all availing themselves sufficiently of the information. I am very concerned about those who are not in the health care loop, who don't have access to health care.

We say to children that they should not abuse substances, alcohol, drugs or smoke because it is not good for their health and yet they don't have access to health care. So we place no value on it and then we tell them it should be important to them. We have a mixed message in terms of our public policy.

Very recently in the President's budget a large cut in the CDC's chronic disease prevention and health promotion programs, appropriations would be reduced by $57 million or 8 percent. It seems to me a foolish cut because prevention is our least costly approach to a healthier America and contributes to the quality of life at the same time as it saves money.

I think if we want a healthy country, we have to make that a priority across the board and have reasonable prospects for access to quality health care for all Americans. What information we do have should be disseminated and promulgated, but many of us have family members who would never have known they needed special care if they had not gone in for their checkup. If you don't go in for the checkup, then how can you be healthy? It is a vicious circle in my view.

For our seniors, if they had access to prescription drug benefits where they could predictably have access to the therapies they need without question as to whether they are going to be able to afford them, I think we would have a healthier older population as well.

I appreciate the concern my colleague raised, it is a legitimate one but the answer is, I think, multifaceted.

I have a couple of specific questions for our witnesses. For Dr. von Eschenbach, I may submit a question for the record when I have more information available to me because I came directly from another meeting. Could you say something about what you are doing at the Cancer Institute on brain tumors? Is there some new initiative there you could speak to?

TRANSLATIONAL RESEARCH

Dr. VON ESCHENBACH. We have been particularly interested in fostering a program that relates to today's topic of bench to bedside, i.e., translational research and the creation of SPORE programs which are specialized programs of research excellence that will enable us to bring basic scientists as well as clinicians together to not only investigate the causes with regard to brain cancer but also be able to translate that into opportunities for therapy. The translational piece of that would be accomplished through our cancer centers and SPORE programs.

Dr. KIRSCHSTEIN. I would like to ask Dr. Penn from the Neurological Disorders and Stroke Institute to expand on that.

Dr. PENN. With the National Cancer Institute, we are working on a little more at the basic end, so we have a program to identify the brand new genes present in brain tumors. In a single type of brain tumor, unfortunately the most devastating, the glioblastoma, there have been found over 1,500 brand new genes. We are displaying these on a chip, a small arrangement where you can look at the DNA in these genes. We expect to find what they really produce in terms of proteins.

Meanwhile, our field out there is ahead of us, and several of the investigators have used this sort of information to say this tumor is ready for surgery and radiation and this one is going to be terrible to treat—same tumor, but different genes.

Finally, we have a program with the National Cancer Institute in our intramural programs at the Clinical Center which are using this information and trying brand new therapies that we think may work. A glioblastoma has about a year and a half total survival, and some of the childhood ones are just as bad or worse. I am very grateful that we can collaborate with the National Cancer Institute on this.

BIOTERRORISM

Ms. PELOSI. Dr. Fauci, as you know, we all stand with the President in the fight against terrorism and support his initiatives on funding for bioterrorism. In your research in your statement, are you getting additional funding to do that or is that money you have to take from other research?

Dr. FAUCI. No. As a matter of fact, it is all new money. It is a rather large increase in our budget designated for work on bioterrorism. There is actually a $1.5 billion increase. We are not diverting anything from the other issues, not from HIV/AIDS or from emerging diseases or from our immunology and immune-mediated diseases portfolio.

Ms. PELOSI. You have been able to absorb this additional money?

Dr. FAUCI. Yes. We have already put together a rather comprehensive strategic plan as well as a research agenda that will guide us towards the effective spending of the money over the next year. I have a copy of the research agenda that we have developed for the fiscal year 2003 resources we are getting.

HIV/AIDS

Ms. PELOSI. That is great. Could you comment briefly. Although the new infections in HIV and AIDS has plateaued, there is disturbing data that HIV infections have increased in inner city minority populations and in young gay men. What more do we need to do to prevent new infections?

Dr. FAUCI. I think it absolutely critical and as a Nation, we are making steps in that direction, to address in a very open and transparent way, what is happening particularly in the inner-city areas. Although the 40,000 new infections each year are constant and disturbingly so, we get into a complacency where we have plateaued but we have plateaued for the last 11 years and it has not come down. What has happened is it has gone away from the generally white gay population in which the infections initially predominated now to an ever-increasing relative proportion of inner-city, minorities, African-Americans and Hispanics, associated initially with injection drug use, but then secondary to that, heterosexual transmission particularly among adolescents.

The other issue that we are trying to address and we are partnering not only with the leaders of the African-American community but particularly with the clergy of the African-American community is the fact that gay African-American men need to be better accepted not only for their homosexuality so they can come out and get access to the care you are talking about but also for the dissemination of information in a way that gets to them and does not allow them to feel marginalized.

We have a lot of societal issues that are responsible for the disproportionate turn of infections towards the inner-city, towards minorities and particularly young minorities.

HIV VACCINE

Ms. PELOSI. Dr. Fauci, I was pleased at your reference to the new HIV vaccine, the progress. I think you mentioned the prospects for that new vaccine?

Dr. FAUCI. We have as a field been looking at different concepts to induce as potent an immune response as possible before moving on to the larger Phase 3 efficacy trial. Some of the concepts I actually mentioned to this committee last year and the year before were just in what we called the pre-clinical phase. As we had hoped, they have moved from the pre-clinical to the animal phase and now are in humans. One approach is taking a common virus to use as what we call a vector, we work well with this virus, it has been in the population and we have vaccines against it, a common virus called adenovirus.

You insert the genes of HIV into the adenovirus and then vaccinate the individual against this common virus which is now mimicking the HIV virus without any of the dangers of HIV infection. The results that were reported in Seattle a couple of months ago indicate the level of immunity, the depth and breadth of the immune response with that candidate vaccine is better than anything we have seen with any of our other candidates.

CANCER AND THE ENVIRONMENT

Ms. PELOSI. Dr. Spiegel, I am well aware of your great work and the turf you cover. I am very proud of your work and it is so exciting seeing what you have done.

Dr. von Eschenbach, if I could ask a brief question about cancer and the environment. In Marin County in an area near San Francisco, you have heard the story before on Long Island and Cape Cod and in San Francisco, there seems to be more than a coincidence of breast cancer that seems to be unaccounted for. We can understand some of the level but some of it seems to be related to the environment.

Can you talk about anything that you are doing at the NCI to see what the connection is?

Dr. VON ESCHENBACH. One of the most important initiatives that has been underway and will continue to be promoted is the understanding of the gene environmental interaction so that how these environmental factors actually cause the genetic alterations that give rise to cancer, in addition to continuing to do our population based studies to identify what those factors are in the environment that are specific for individual types of cancer. It is a multi-pronged effort.

Ms. PELOSI. In Marin County, it is not an environmental justice issue but in some parts of our country, it is, in areas where there are chemicals in the air. For one reason or another in San Francisco, it is certainly an environmental justice issue because it is in the poor neighborhoods, minority neighborhoods. I would encourage you in that direction because the bench of course is essential to our success but I think beyond the bench and looking at the environment may have some answers for us.

Thank you all very much. Dr. Kirschstein, always an honor for us when you are here. Thank you for your excellent work. I hope we will continue to see you along the way.

Dr. Hodes, I neglected you today but I will catch up later. This aging question is very sensitive with some of us.

Thank you.

Mr. REGULA. Mr. Jackson.

PREVENTION-INTERVENTION COMPONENTS

Mr. JACKSON. Thank you.

Let me begin by thanking the various directors for their outstanding work they continue to do.

I have four questions and I am going to ask one of Dr. Penn, one of Dr. Spiegel and two of Dr. von Eschenbach.

Dr. Penn, stroke, America's number three killer and leading cause of permanent disability, disproportionately strikes African-Americans. As I understand it, African-Americans have a 38 percent greater risk of first strokes than whites. Compared with whites, young African-Americans have a two to three times risk of clot caused strokes and African-American men and women are more likely to die from stroke.

Can you please tell us how NINDS is addressing health disparities in stroke?

Dr. PENN. I started before, but I will really flesh it out this time. We are very concerned and are working through our specialized neuroscience research programs to develop what we are calling "prevention-intervention" components. We have engaged our investigators, because we have five or six grants out there for the studies of stroke in African-American populations both in Chicago and Baltimore, and our flagship, which we are trying to launch right now, is at Morehouse School of Medicine in Atlanta where we are in the middle, as we said last year, of the "buckle" of the stroke belt. We are looking at both populations, minority and majority.

That is coming along very well. We have a lot of help from stroke investigators, from Dr. Sullivan who is the President at Morehouse, and a lot of help from the Surgeon General. What we are trying to do is not only work on prevention- and there we will have help from the National Public Radio people in Atlanta, on all the risk factors, but also on intervention. African-Americans have a somewhat different profile and don't have clots in the neck as often as they do in the head, so we have to work on why. There are a lot of things we have to address.

We work as closely as we can, and have from the beginning, with Dr. Ruffin and his group and also with Dr. Judy Vaitukaitis in the National Center for Research Resources, because she provides a lot of infrastructure in all of our programs.

DIABETES RESEARCH WORKING GROUP

Mr. JACKSON. I am going to read the final three questions so the respective heads can respond. Dr. Spiegel, it seems the Diabetes Research Working Group has provided an important road map for diabetes research since it was released in 1999. I am interested in what plans you have to update this report in the future.

Dr. von Eschenbach, as you know, medically underserved communities and minorities are disproportionately affected by cancer. To begin to effectively address this problem, it seems important to develop expertise from within the community. Recently, I read that you had spoken to your advisory board about your plans to revamp the National Cancer Institute's Cancer Center Program and focus on minority and underserved communities.

Currently, are there any cancer centers at minority serving institutions?

Secondly, when you headed the Integration Panel for the Department of Defense Peer Review Prostate Cancer Research Program, you recognized the need to accelerate research and training at institutions serving minority populations. The DOD Prostate Cancer Program has designed interesting initiatives that would create partnerships for historically black colleges and universities in order to enhance the research capital within the institutions serving the black community.

During the past two years, I regularly noted the slow pace at which the NCI Center to Reduce Health Disparities has undertaken new initiatives. I am wondering what specifically are NCI's plans to reduce the burden of prostate cancer in the black community? Will NCI support increased training and research initiatives for minority researchers and historically black colleges and universities?

Dr. Spiegel.

Dr. SPIEGEL. In 1999 the Diabetes Research Working Group issued a congressionally mandated report in which it identified five extraordinary areas of opportunity: the genetics of diabetes, autoimmunity and the beta cell, cell signaling, obesity, and clinical trials. All the Institutes of NIH, and the Diabetes Mellitus Interagency Coordinating Committee that I chair, have been addressing these five extraordinary opportunities with all the resources we have.

Congressional language we have in this fiscal year asked us to do an update of this very important report to define the progress since the report which was issued in 1999, to define the initiatives we have put in place, and also the new opportunities.

To do this report, due August 31 of this year, we have consulted widely with the community, both by bringing in outside experts from around the country with whom we will be meeting on May 16, and by interacting closely with our constituencies, the American Diabetes Association, the Juvenile Diabetes Research Foundation, and with patients and their families as well.

I and my staff clearly need to hear directly from the patients. With the synthesis of all this input, we expect to have a very complete progress report for the Congress.

CANCER CENTERS AND TRAINING

Mr. JACKSON. Dr. von Eschenbach.

Dr. VON ESCHENBACH. With regard to the issue of training, I think you touched on an extremely important issue that I am very pleased to have Harold Freeman within the National Cancer Institute to head up our Center for Minorities and Health Disparities. In recent conversations I have had with Dr. Ruffin, what we really are very much looking forward to is the opportunity to enhance the pipeline that will bring young investigators at the college level into the biomedical and medical research arena and to provide a pathway in addition to continuing to support their career development once they have received their degrees. I think the training issue that you allude to is an extremely important one.

With regard to Centers and SPORES, we have within the prerequisites for the designation of centers and SPORES the expectation and review process to be certain that within those programs there are outreach to minority communities so they are included and incorporated into those centers' efforts. With regard to the centers and the training, both of those are initiatives that need to be further enhanced.

Mr. JACKSON. Dr. von Eschenbach, I look forward to working with you and coming up with some creative ideas on how to enhance those.

Dr. VON ESCHENBACH. I think the point that you have alluded to is an extremely important one in that one of the personal particular philosophies that I have is that we need to do this in a partnership with the community so that we are working collaboratively together because I don't believe we can simply impose or superimpose solutions. These need to be collaborative strategies that we will develop together.

Mr. JACKSON. Thank you.

INFORMATION DISSEMINATION

Mr. REGULA. Dr. Kirschstein, I would like an idea of how you disseminate this information? There is a lot of constructive information available here. How do 280 million Americans access it?

Dr. KIRSCHSTEIN. Each of the Institutes and Centers at NIH as well as centrally through my office has an Office of Communications of health information. A great deal of that information is communicated to the public through documents that are specifically prepared for public usage. Let me give you a quick example not among the Institutes that is here and ask each of them to address it.

In the Heart Institute, they have books on healthy diets for people to prevent heart disease and to prevent or ameliorate heart disease and the booklets are published in English in laymen's terms as well as in Spanish.

Mr. REGULA. How are they distributed?

Dr. KIRSCHSTEIN. They are distributed broadly to radio stations, television stations, public libraries, schools, community centers and in addition, we have mandated programs in hypertension education and cholesterol education, that go out to the public generally. I would like to let the Institute directors describe how they do that.

Dr. VON ESCHENBACH. With regard to the Cancer Institute, it really is a multifaceted strategy that begins with our internal process of communication with regard to the creation of a website so that patients and professionals have the opportunity to immediately access information.

We have also funded a very important initiative over time called the Cancer Information Services which provides a network in various institutions so that there can be opportunities for patients to call in and get information about specific concerns and issues that they have.

I understand within the past year there were 1.9 million of those kinds of requests for information.

Then there is the wide dissemination in print and visual media of cancer information publications. There were 10 million of those publications that were distributed. So it is a multifaceted strategy.

In addition to that, as I indicated earlier, we also are spending a great deal of effort in trying to do the research to understand how to most effectively communicate with all levels of our society so that we formulate messages that are appropriate to each of the segments affected by cancer.

Dr. FAUCI. We have somewhat similar mechanisms to disseminate information that range from written material to a very comprehensive and updated website that is accessible to the general public.

Mr. REGULA. What troubles me is a lot of Americans don't have a website.

Dr. FAUCI. I got you. For those who don't, we have a series of well orchestrated outreach approaches, particularly the town meeting format that we utilize a lot. Some examples of that, Ms. Pelosi remembers how we did that together in the San Francisco area when we were trying to get out information vis a vis HIV/AIDS, not only in the early years but as the therapies became available.

We recently had a town hall meeting type approach here in Washington at the 19th Street Baptist Church in which we addressed many of the issues that we were talking about and how to engage the minority community about embracing the African-American clergy. This was a sponsored town meeting by the clergy in the District of Columbia.

So we do everything from the sophisticated thing that not everybody has access to, to actually going out in the community and talking about these issues. We have done it with everything from HIV/AIDS to asthma, we have a number of outreach programs not only in NIAID but also with the National Heart, Lung and Blood Institute and the National Institute of Environmental Health Sciences, a number of outreach programs vis a vis education of asthma and interventional components of asthma that have been an important part of our inner-city asthma programs. So it is everything from websites to going out into the community.

Dr. PENN. We pursue all the avenues that you have already heard. I should mention that we work pretty closely with our professional societies, who are into this also. We are all available, all of us staff who are physicians and not physicians, to go out with our voluntary organizations and go to various chapter meetings and national meetings and talk about what we can disseminate in terms of prevention information or what we are doing.

Stroke is an excellent example of that because we had recently the "Nightline" program, which some of you may have seen, where the producer actually had a stroke, and through the new information on the plasticity of the nervous system, he worked his way, literally exercised his way, back to being essentially normal. This is something that is going to come in the next 10 years, I hope, when we know more about why that happens.

We had a "Stroke Sunday" which was very effective; we have to go into the churches like this.

Dr. KIRSCHSTEIN. Let me add a few comments. First of all, we work very hard at this. We are all available as the directors have already described to come to any place in the country that wishes to have us and we will volunteer. Mr. Obey had a number of us on four different weekends. Dr. Varmus was Director, I was there as the Deputy Director and so many of us have been to those districts. In addition, in the local area which includes Virginia, Maryland, Pennsylvania and the District, most of the institutes have adopted elementary, middle schools and occasionally high schools and go into those schools to teach the children. This gives us an opportunity particularly for diverse populations, in Virginia, for example, a very diverse population, of the largest growing immigrant group of Vietnamese to talk about what they can do to be healthy.

Dr. HODES. If I could just add, in addition to Dr. Kirschstein's statement of our willingness to help, there is also an enormous resource in the large cadre of physicians and scientists who are supported by the Institutes and who are in institutions across the country. Working with you, we are happy to and often do direct attention to them as wonderful resources in various areas of the nation.

Dr. SPIEGEL. Let me give you an example of another unique kind of program we are just starting because this problem of type 2 dia-

betes disproportionately affects Native Americans. We have launched a program in partnership with tribal colleges and universities where we have a dual goal. We are trying to create a science curriculum for tribal middle schools and high schools in which science education will be focused on diabetes. On the one hand, participants will receive health care information they can use. As Dr. von Eschenbach implied, we are partnering with the tribal colleges and universities, so we are not just superimposing this information from the outside. By partnering with them in a culturally sensitive way, we hope that we will inspire some of these students to themselves become researchers and ameliorate the diabetes affecting their tribes.

Dr. KIRSCHSTEIN. All of this said, we need to keep working at it. It is something we have to continually emphasize because people have short memories and if we don't go out and continue to do this, the messages will not remain with them.

Mr. REGULA. If you had a publication that lists what you have available and the Administration on Aging could distribute these with meals on wheels to the area aging centers so a senior could pick up this pamphlet if they are interested in stroke and see where to send to get the pamphlet, stroke, diabetes, whatever they check off, mail it in and they would get it return mail. Would that work?

Dr. KIRSCHSTEIN. I think it would and we will start on it right away, Mr. Regula. I really do think it is a good idea.

Mr. REGULA. You hear so much super excellent information in these hearings and I keep thinking how do we get it to the people because that is our primary concern.

Dr. HODES. It is a wonderful idea. The National Institute on Aging interacts closely with the Administration on Aging precisely for the reasons you indicate. They are an avenue to communicate with a large number of older Americans. This is an excellent suggestion which we will certainly incorporate into our interactions with them.

Mr. REGULA. Mr. Miller.

BASIC VS. CLINICAL RESEARCH

Mr. MILLER. I thoroughly enjoy the opportunity to hear you all talk.

You mentioned websites. I enjoy them. I remember just over a year ago I had this liver concern, we had to have a transplant with our daughter who donated. I went to your website, Library of Medicine, and Dr. Lindbergh is not here today but there is so much available, so much that goes over my head and some of it you can't get to. When you go to the New England Journal of Medicine, you have to be a subscriber to it, so you don't always have access to it and I can't always understand it but you do have good web pages. You are right, a lot of people don't have access to it but their friends do. I think that is a great way to make that information available.

I have a concern with basic research versus clinical research. You mentioned Dr. Hodes you need to educate the medical community, the physicians and such that basic research, we have seen a decline in the amount of money for basic research versus clinical.

Nancy Pelosi talked about who takes charge of the education of lay people. We visited the CDC a few years ago and talked about diabetes. Our former Speaker, Newt Gingrich, was really concerned about that. There was a question about education to prevent diabetes, diet and such. I wish we could spend more on that area. You could prevent so much by education. How do you get out that message? Whose responsibility is it? Is it CDC's? You have an education role but your primary role should be research and sharing that research information. Who is responsible and how do you keep yourself still focused before you become a major teaching institution?

Dr. KIRSCHSTEIN. It is a fine line but we feel it is a responsibility. Actually, we have an inherent responsibility because the American public has so much interest in research and the Congress has provided us with so much wherewithal to do this that I feel, and I think all my colleagues do, it is an inherent responsibility on our part, in addition to concentrating on the areas that you are mentioning, Mr. Miller, to go the next step.

Incidentally, we try very hard to make this understandable. One of the things that has happened is that the media has been superb at this. The most important findings in the New England Journal of Medicine are translated most often into newspaper articles the day before they are published in the Journal.

Dr. HODES. To comment further, this balance between basic and translated clinical or applied research, I think today's theme is an excellent way to address that. We all continue to have the obligation to determine the appropriate balance between basic and applied research and to make that tailored to the circumstance.

At an extreme, if we dealt only with application and neglected basic research, we would mortgage our future in terms of developing new generations of interventions. If we were to do the opposite and focus solely on basic research and not translate it, that would also be irresponsible.

I think when we report to you or you see published a percentage in basic or clinical research, this is really an outcome determined by scientific opportunities and public health imperatives. If there is a finding in an area of basic science that has a compelling potential for translation to clinical research, then you will see a shift in that area towards more clinical research. If there is an area in which the basic understanding doesn't yet allow translation it is predominantly basic. I think we are constantly examining the profile broadly but also in each particular area to make it best serve both the long and balanced short term obligations we have.

Dr. SPIEGEL. I would just point out also that one shouldn't make too large a distinction between basic research and clinical research. Although we are emphasizing "bench-to-bedside," it goes in the other direction as well. Let's look at the Crohn's disease discovery that I mentioned. This new susceptibility gene as been determined, that was found through clinical research focused on identifying people with Crohn's disease, studying their families and then being able to do the genetic analysis. Now that the new gene has been discovered, one needs to go back to the laboratory bench, because it had never been understood or even appreciated before. This genetic discovery offers a whole new pathway for which critical drugs

may be developed for either prevention or treatment. Research needs to be a seamless interaction, a bidirectional interaction. That is the vision we really have.

Dr. VON ESCHENBACH. I was just going to add, Mr. Miller, that your point about the dissemination issue, I think one of the important lessons I learned early on as a surgical oncologist was I could not solve the problem of cancer alone. It had to require collaboration and integration with others. I think that is particularly true today of us as an institution, that we need to be collaborating not only among ourselves for this exchange of information but also outside. The national dialogue on cancer, for example, recognized that cancer is a societal problem and we need to come together with the CDC, with other Federal agencies, and with the States in order to really be able to approach this problem comprehensively.

I think the National Cancer Institute has to contribute its unique piece but we also have to collaborate and work effectively with others to make sure we are certain the entire agenda is being addressed.

HIV/AIDS THERAPEUTICS

Mr. MILLER. We have to communicate to the American people what a great, crown jewel we have and part of it is to see how they relate. What Dr. Collins has done is great but it is hard for others to comprehend what that really means.

I have one other question. I want to switch back to Dr. Fauci. I am sorry Ms. Pelosi is not here because it is a continuation of her question about HIV issues. When you go through Phase I, II, III trials and then it is available basically. Tell me about how long it takes to go through these trials? I guess there is no rule of thumb and some go pretty fast. The last big breakthrough was Protease which was quite a few years ago. I don't know when Protease came out or got approved but it was six or seven years ago.

What is in Phase III? You said the latest was a Phase I issue which could take years.

Dr. FAUCI. I was referring to vaccine, you are referring specifically to therapy now. Let me address that. As a concept, the protease inhibitors were tested in 1995, became available in 1996, so we have had about 5½ years of the concept of protease inhibitors being used in our regimens for HIV together with the nucleoside analogs and the non-nucleoside analogs. Typical examples of a nucleoside analog is AZT or DDI or DDC.

Right now, the two exciting areas of concept breakthroughs are the other two vulnerable sites of the virus, vis a vis its replication. One is its binding to the surface of the cell and there are a number of drugs that are called fusion or entry inhibitors. They prevent the fusion of the virus to the cell. The way HIV gets into the cell, it binds to a receptor the way most viruses enter cells. There is a receptor that they capture or co-opt, then HIV enters the cell.

These agents are already past Phase I, well into Phase II, and now we are planning to collaborate with some of the companies involved in going into Phase III trials for a class of fusion inhibitors. One that is the furthest ahead is from a company called Trimeris from Research Triangle Park in North Carolina. The agent is called

T–20 for Trimeris 20. It will get a name when it gets licensed by the FDA.

The other concept is the integrase inhibitors. They are just going from pre-clinical into Phase I trials. The integrase inhibitor prevents the virus, when it converts to its DNA form, from inserting itself or "integrating itself" into the chromosomes of the cell.

With those two concepts, you have the spectrum of what you are referring to, Mr. Miller. You have the fusion inhibitors that are already going into Phase III which means that in a period of one to two-and-a-half years, they will be ready for licensure if they are accepted. Then you have the integration inhibitors which are just going into Phase I.

In a normal, accelerated format which is what we have been using successfully with HIV, it generally takes from the time you do it in pre- clinical studies to the time you get licensed anywhere from four to five years, in comparison to 12 years the way it was decades ago. So it has cut the time frames by more than half.

Mr. MILLER. Two new areas have the potential to be the next generation of drugs?

Dr. FAUCI. The next generation of drugs for HIV, yes.

Mr. MILLER. Thank you.

INTRAMURAL STRUCTURAL BIOLOGY

Mr. REGULA. One of you used the word intramural. Do you move information back and forth at NIH, so that you might discover something that has a relationship to what you do? Is there a cross-cutting, maybe that is the word?

Dr. KIRSCHSTEIN. I will let the Institute directors describe that but I think the most remarkable way is they all talk to each other and their scientists talk to each other all the time, the informal communication in addition to the formal scientific seminars and so forth. I will let them expand on that.

Dr. SPIEGEL. I have asked Dr. Fauci's permission and he says it is okay. He just mentioned the integrase. We have in the Intramural Program, which represents roughly 10 percent of the budget that is expended on research in Bethesda and some outlying campuses, some of the best structural biologists. These are the people who determine the three-dimensional structure of different proteins. It was actually individuals in the National Cancer Institute who were some of the first to determine the three-dimensional structure of the protease of HIV. In the early 1990s, scientists in the NIDDK Intramural Program determined the three-dimensional structure of HIV integrase. There is an AIDS-targeted program in the Intramural Program and it is a very collaborative program. That three-dimensional structure allowed drug development of the kind you now see moving forward appropriately in the Extramural Program. Tremendous collaboration and interaction at many levels move the research agenda.

HORMONE RELATED STRESS

Mr. REGULA. That is interesting. Incidentally, talking about this pamphlet, you ought to get those into doctors' offices too. They would be more interesting than most of their magazines. The way

you have to wait in these places these days, it would be a great opportunity to disseminate.

I was a speaker on a panel in Phoenix for the Steel Institute. I was waiting on the fellow speaking ahead of me. He had been the Director of the Medical School at the University of Nebraska. He had a heart attack at 43, no family history and he finally concluded it was stress induced. He decided to spend the rest of his time focusing on stress. He had an institute in Phoenix, wrote a book, "It's not Worth Dying for." Maybe some of you are familiar with it.

I would be interested to hear from each of you what role stress plays in health because obviously it has to get your system out of whack if you are stressed. What do you think?

Dr. SPIEGEL. First, one needs to be a little cautious about invoking stress as a cause of disease. Undoubtedly, it is important, but for historic reasons, one should be cautious. In the 19th century before the discovery that a particular bacterium caused syphilis, stress was attributed as the cause. Peptic ulcer disease was thought to be caused by stress and then investigators determined that a bacterium, *Helicobacter pylori* is the cause. This is another example of collaboration and interaction between our Institute which supports gastroenterologists, and Dr. Fauci's Institute, the National Institute of Allergy and Infectious Diseases, working. We actually co-supported study of infectious etiologies of chronic diseases of unknown cause.

On the other hand, there certainly is an adverse effect of stress and, as an endocrinologist, I know that it comes through the hormone system. Specifically, the steroid hormones, the so-called glucocorticoids, have a very adverse effect in terms of breaking down protein and increasing obesity, particularly central obesity. There are some plausible notions that stress may have an impact in terms of obesity in the general population. We should always investigate these concepts with careful research and scientifically, before attributing conditions to stress.

Dr. FAUCI. I second that and it really gets back to the causal etiology of a disease versus what we call co-factors that might either predispose or impede someone's capability of dealing with the true primary cause of disease. We often see that in situations and it relates to what Dr. Spiegel said vis a vis glucocorticoids which also have a rather profound suppressing effect on the immune response. So when you are dealing with infectious diseases which require an appropriate response of the host to the microbe, if you don't have a microbial infection, if you don't have a microbe there, you could have all the stress you want and you are not going to get an infection. It is the same as saying does going out in the cold give you a cold? You could freeze to death before you get a viral illness if there is not a virus there.

When you do come into contact with a microbe, the host response is not infrequently tempered by the state of your ability of your immune response. If you are under severe stress or severe exhaustion, some of the natural body's defenses that would allow an otherwise normal person to very easily clear that infection might be impeded so that an infection you would otherwise handle well wreaks havoc with you because you have a suppressed immune system on the basis of the mechanisms that Dr. Spiegel mentioned.

Dr. VON ESCHENBACH. One of the amazing comments is that the story in cancer is almost exactly the same story Dr. Fauci just told you. We know there are certain things that cause a cell to become a malignant cancer cell but the behavior of that malignant cancer cell is dependent upon the environment it finds itself in. The body that cancer is in has an effect on that cancer. Stress, nutrition, a variety of other things may be affecting the person and that then influences the behavior of the cancer. So stress doesn't cause cancer, but it can very much play a role in how the cancer may behave.

STRESS

Dr. HODES. In terms of the effect of stress on the nervous system, I think there are lessons learned from research and Dr. Penn may well want to comment too. One has to be careful not to regard stress a linear determinant, saying stress is bad or stress is good. In terms of stress response, it is not surprising when one thinks about the way in which our species evolved, acute stress responses to specific circumstances are very adaptive. If you need to flee under an emerging situation, then a stress response is appropriate and that sort of acute stress response in the nervous system does not appear to have harmful effects. However, chronic stress has a quite measurable adverse effect on brain structures that can now be detected.

Moving from that basic neuroscience example to a case of practicality, one of the chronic stresses that is of increasing importance in the aging community is that which caregivers experience, caregivers for individuals with Alzheimer's or other disabilities. An extensive series of studies now have shown that those individuals undergoing that kind of stress have measurable changes in their immune response system and importantly, interventions including respite or physical exercise programs in populations of these caregivers appear to measurably reverse that stress.

Stress can be good in the right situation, often in excess is bad, but importantly, there are ways it can be addressed therapeutically.

Dr. PENN. Just a couple of corollaries. What is called the "flight or fight" situation, when you really are at what you would call maximum stress, involves a very important part of the nervous system called the autonomic nervous system, which makes you perspire, makes your pupils dilate and so on. This is one of the places the nervous system interacts with the immune system, because it isn't just the circulating hormones of the adrenal gland, it is also the autonomic nervous system that may trigger that reaction and certainly regulate with it up and down.

Again, all of us are working together.

Dr. KIRSCHSTEIN. Mr. Regula, we have five Institute directors. I am sure every one of the others could give you an example and the important one when he comes next week or the week after in heart. Dr. L'Enfant, I am sure will want to address that.

Mr. REGULA. The Speaker at 43 had a heart attack, no family history, his parents in their 80s. Then he realized he was fighting with the board of trustees, trying to raise money, jumping on airplanes and he felt that his heart attack had been stress induced.

Dr. KIRSCHSTEIN. I think it is probably more complex than that. Dr. L'Enfant might want to explain that to you because it has similar situations to what have been described, I am sure. I think it is an important phenomenon that we all must take into consideration.

Mr. REGULA. I will never forget he gave us the three rules. He said, one, don't sweat the small stuff; two, most things in life are small stuff; and three, if you can't fight and you can't flee, flow. Pretty good advice.

Dr. KIRSCHSTEIN. Very true.

GLOBAL RESEARCH

Mr. REGULA. I must say I watched President Reagan and he practiced that. He may not have known he was doing it but I remember his famous quote, "Doc, are you a Republican" when he was sitting there, grating with a bullet, so he was flowing, I think.

Dr. Fauci, you have a tough job of translating research globally because infectious diseases are everywhere and it is the leading death around the world for those under age 45. What are the barriers associated with the translation of research on a global level and how do you overcome them? You are the institution for the world. I don't think 5 billion people appreciate it but you really are.

Dr. FAUCI. One of the arenas you are referring to, and as you said, each of the Institutes could probably give their own example, is because of the global-nature of infectious diseases, given our responsibility for infectious diseases, we often find ourselves in interactions at the international level.

One of the things we have learned over the years, and I think there has been a good lesson, that if you are going to translate the kinds of advances that we make in the United States that would be most applicable and relevant to developing nations, particularly the work we do in vaccines and therapies, when you engage developing nations, you have to engage in true partnerships where you don't just as we say practice parachute science where you parachute in, do your thing and you leave. You have to build as we have, particularly in the research arena, what we call sustainable infrastructure so that when you leave the country, you will have trained the in-country investigators, you will have put into place the opportunity for them to continue without you and not to essentially dissipate when you leave.

That has been the fundamental philosophy that has driven our networks of prevention trial networks, vaccine trials networks, our centers for interdisciplinary research internationally in infectious diseases. We have a wide array of networks, and are driven by the fundamental philosophy of collaboration and building sustainable infrastructure. It is really starting to show to be quite successful.

RESEARCH COLLABORATIONS

Mr. REGULA. Do all of you have contacts with institutions beyond our borders and do you get a pretty good partnership type response?

Dr. KIRSCHSTEIN. Yes, indeed.

Dr. HODES. Absolutely, and there are many such examples. Some of them involve specific research institutions, others are with na-

tional organizations. For example, in the area of aging research, there is a lot to learn as well as disseminate by comparisons of what the practices and consequences are internationally, both in developed and developing nations. So there are extensive networks in which NIH participates as a partner.

Mr. REGULA. Do you gain ideas from other parts of the world?

Dr. HODES. Without question. For example, mentioning the trend toward decreased disability in the older population in this country, we are extremely interested in learning how those trends compare with what goes on in other countries and what factors may be responsible for those differences. Not all research can be done easily in a controlled, randomized clinic trial setting. So the natural experiments, comparisons that go on, as well as addressing the diverse needs of a heterogenous world also inform us about issues that are as important to this Nation as they are to the rest of the world.

Dr. SPIEGEL. A lot of this depends on specific disease examples. We deal mostly with non-infectious diseases; however, type 1 or what used to be called juvenile diabetes is very prevalent in the Scandinavian countries. Finland, for example, has the highest incidence. Therefore, it is very important for us as a Nation to partner with those countries that have really terrific health care systems and registries. Also, organizations in the private sector, the Juvenile Diabetes Research Foundation, are able to fund international research much more readily than we are. We can then partner with those investigators.

In fact, our type 1 diabetes Trial Network here in the United States is trying to match up and partner with those outstanding institutions in Europe to speed these trials. That way we can have more patients and get results more quickly. That is just one example.

Mr. REGULA. So you have a relatively free flow of information back and forth with other nations?

Dr. KIRSCHSTEIN. Yes, very. Let me add one thing that has not been mentioned.

All these Institutes and all the others, there is also a Fogarty International Center, one of the 27 centers and institutes and it will be in one of these sessions sometime soon.

Mr. REGULA. Somebody asked me the question yesterday, do you develop drugs or is this done by the industry? We get a whole plethora of new drugs almost weekly. Is that the role of the NIH? I don't know?

Dr. KIRSCHSTEIN. It is complex because there are things NIH does and things the industry does and the Institute directors can describe it.

Dr. FAUCI. A typical example, Dr. Spiegel alluded to. It is sort of a case history that answers your question. The original crystallization of the protease molecule took place at the NIH. That was done in partnership and then the material, the information was transferred to industry. The industry then helped develop the inhibitor of that protease molecule which now we refer to as the protease inhibitor which is a major anti-HIV drug.

The drug companies that did the development of that drug then utilized the NIH's clinical trial networks to prove the drug was safe

and effective and ultimately got approved. What you had was the concept was developed within the Intramural Program at NIH, the actual development of the drug took place by the drug company and the proving of the drug's efficacy was a collaboration between the NIH and the industry.

Mr. REGULA. Very interesting.

Mr. Miller, do you have any other questions?

STEM CELL RESEARCH

Mr. MILLER. One more. The issue we talked about briefly yesterday is stem cell and therapeutic cloning. We are getting into a subject you may not want to have to discuss because of the political.

There was an article in this morning's paper about two papers coming out that adult stem cells may not be as useful as some thought or would have hoped. We still don't know. I am one of a minority within my party and I voted against the bill, banning cloning, banned therapeutic cloning.

Would you all comment about where you stand on grants in the area of stem cell research? We talked about it briefly yesterday, therapeutic cloning potential, trying to block it and ban it in the United States, we don't know where it is leading yet but comment both on where you stand on stem cell research and therapeutic cloning.

Dr. KIRSCHSTEIN. You heard from Dr. Baldwin yesterday that the lines that have been approved, which were there prior to the President's announcement on August 9 and are now listed on our registry. As she told you, we have mechanisms ready and able to put forward funds to continue research on that. She described to you what was going on.

The two papers on adult stem cells which were described in the newspaper this morning are two of many studies that are being done. I think Dr. Spiegel probably has more knowledge of those than anybody else. He may want to comment and then we will move to the next part of it.

Dr. SPIEGEL. The papers are right here from the journal, Nature. It is a very controversial area and a very rapidly evolving area of science. The question is: What is the potentiality of adult stem cells to turn into the many different types of cells in the body? Plasticity is another term that has been applied to it.

Papers in the New England Journal looking at recipients of bone marrow donors, from a brother into a woman, gave some evidence of adult stem cell plasticity. They showed you can just look for the Y chromosome, which the woman won't have, in the liver, in the gut, in other areas that the bone marrow cells from the donor had populated these other areas. That suggests plasticity, but has no implications therapeutically.

These papers are contrasting that view. They are suggesting that some of the apparent plasticity of these adult stem cells is really due to a strange phenomenon where they fuse with other cells. I won't go into it, I am not a stem cell biologist so this is over my head to some extent. What I can tell you is it just reflects the scientific uncertainty, why the research is involved and evolving in terms of the potential plasticity of the adult stem cells versus the unequivocal potentiality of the embryonic stem cells.

Mr. MILLER. The other part of the question was therapeutic stem cells.

Dr. KIRSCHSTEIN. I wanted to make sure no one else wanted to make a comment.

In terms of therapeutic cloning, the Administration has made its position very clear and we support the Administration's position. In terms of scientific potential, the National Academy of Sciences has recently issued a report in which many scientists joined together to study the issues and came up with the recommendation that there is enough scientific potential to go forward on that work. The Academy of Sciences report equally mentioned the fact that the moral and ethical issues need to be discussed widely as this work might, in its view, be started.

It is my feeling at least that needs to be discussed much further.

Mr. MILLER. What is the potential of therapeutic cloning? Where could it theoretically lead? Are we driving researchers off to England where they allow this? We have the potential, the economics of biomedical research has an impact on our economy. Luckily the Senate is not going to pass anything but they don't pass anything anyway. I don't want to put you on the spot because you report to the President.

RESEARCH WITH DRUG COMPANIES

Mr. REGULA. Report to the Administration. One question, Dr. Fauci, on the drug issue.

Do you have contractual arrangements with these drug companies? We spend a lot of taxpayer money on research through the grants and so on. The drug companies pick up from there. Is this based on contracts?

Dr. FAUCI. It really is on a case-by-case basis. One of the mechanisms of interaction and collaboration is by what we call a collaborative research and development agreement. When you engage in a CRADA agreement, resources are put in by both sides, and what usually spins off is if there is intellectual property, for example if a patent is issued, is a shared patent depending on the contribution of each. Then the companies can get exclusive licensure if they are very much involved.

Dr. VON ESCHENBACH. In addition to the mechanisms Dr. Fauci already alluded to, that the NCI is involved in as well, we are also exploring at this point collaborative relationships with the pharmaceutical industry to co-fund clinical trials so that they would contribute half of the cost for a series of programs. That mechanism will hopefully be able to be implemented through the Foundation for the National Institutes of Health. We are looking at these collaborative public-private partnerships at a variety of places along that continuum from discovery to delivery.

Dr. HODES. Just to comment further. Exactly that arrangement through the Foundation is already in place in one series of collaborative research in which a number of the Institutes, the Arthritis Institute and Aging taking the lead, have partnered with four major pharmaceutical companies who are investing millions of dollars to co-fund clinical studies in this case in the area of osteoarthritis and interestingly are doing so under circumstances where

they were willing to contribute in the absence of any intellectual property advantage to themselves.

This may not be the rule, being realistic, but there are occasions in which such partnerships agree in what is perceived to be the common good without contractual assignment of intellectual property rights.

Mr. REGULA. We will have questions for the record. You all have been terrific. I wish all of America could sit in on this. It would make them feel good about what is happening with their tax dollars at NIH. We could go on much longer because it raises a lot of interesting questions but I looked at my schedule and I think if we don't terminate, we will all get stressed. [Laughter.]

Mr. REGULA. The committee is adjourned.

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

PARTNERING WITH THE PKD FOUNDATION

Mr. Young: Dr. Spiegel, your Institute has benefitted from significantly expanded resources allocated to NIH over the past several years Would you tell us how NIDDK partners with private funding sources to enhance the resources available for research to expand its mission to find cures or ameliorate the impact of lifethreatening diseases, such as polycystic kidney disease? I would appreciate learning about any efforts the Institute has undertaken with private funding sources to expand clinical research on polycystic kidney disease.

Dr. Spiegel: The NIDDK has a long history of partnering with the private sector, both with patient advocacy groups and pharmaceutical firms. The NIDDK accepts monies as either Conditional or Unconditional Gifts. Conditional Gifts may be allocated to a specific disease or area of inquiry. The NIDDK also accepts Unconditional Gifts, which may be used at the Institute's discretion. Such funds may be awarded to investigators directly or may be used to defray the costs of scientific conferences and meetings. For example, the NIDDK recently partnered with Monarch Pharmaceuticals in the African American Study of Kidney Disease and Hypertension.

With regard to PKD, the NIDDK's Division of Kidney, Urologic, and Hematologic Diseases is partnering with the Polycystic Kidney Disease Foundation to support a clinical trial into therapies. The Institute recently accepted a gift in the amount of $584,000 from the Polycystic Kidney Disease Foundation. This most generous gift will be used to assist in the funding of pilot and feasibility studies at the four Participating Clinical Centers taking part in the "Polycystic Kidney Disease Clinical Trials Network." The funds provided by the PKD Foundation are over-and-above the amount of funding to which NIDDK had committed for this project; in other words, these monies will not be used as replacement funds for NIDDK grants but will enhance research efforts. This Clinical Trials Network will design and carry out a clinical trial to identify strategies and therapies aimed at slowing the progressive loss of renal function in people with PKD. Applications are currently under review, and awards are planned to be made following the May 2002 meeting of the NIDDK's National Advisory Council.

Mr. Young, you may also be interested to know that the NIDDK's PKD research effort is being strengthened by new work on mouse models and on basic cell biology, in order to understand the cause of disease and to facilitate testing new treatment interventions. These efforts also reflect partnering with the PKD Foundation. Four centers for basic research on PKD have been established. Another recent initiative – the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) – has promoted the development and testing of improved state-of-the-art imaging methods for PKD, including CT scans. The NIDDK is now expanding its support for both technology development and improved image processing.

The NIDDK's goal is to ensure that results emerging from studies in basic research, technology, and clinical trials of treatment approaches will complement each other to improve the lives of PKD patients as quickly as possible.

FY2003 REQUEST FOR NIMH

Mr. Istook: Dr. Kirschstein, what efforts are underway at NIH and NIMH to focus greater attention and resources on promising research at the basic, clinical, and services levels on severe mental illness such as schizophrenia, bipolar disorder and major depression to ensure that advances rapidly translate into better treatment and service for individuals living with these illnesses? How much is specifically being spent on research specifically targeted to Traumatic Brain Injury?

Dr. Kirschstein: In keeping with the overall mission of NIH, all research supported by NIMH has relevance to an improved understanding of mental disorders; still, several major research thrusts now underway are directing unprecedented attention and resources to activities assigned to improve treatment and services for mental disorders both at the individual clinical and public health levels. The generation of knowledge that will lead to improved care for persons with mental disorders constitutes the core of the NIMH's scientific and public health mission, a mission that gained urgency with the conclusion of the WHO/World Bank/Harvard School of Public Health Global Burden of Disease study that mental disorders account for four out of the leading ten causes of disability worldwide, with depression the first-ranked cause of disability in economically developed nations. Accordingly, a key NIMH initiative is the preparation of a Research Strategic Plan for Mood Disorders, primarily major depression and bipolar disorder. Over the course of the past year, NIMH staff, working with 130 extramural/intramural scientists and public representatives, have analyzed the most current knowledge and research on mood disorders in ten broad areas of science, ranging from genetics to service delivery. The plan outlines the goals and implementation steps to be taken to advance our understanding of the brain, human behavior, and specific pathology involved in depression and bipolar disorder. The plan, which will serve as a prototype for future disorder-specific strategic planning efforts, will set goals for developing new treatments and enhancing access to appropriate and effective treatments.

The very structure – and thus the operational capabilities – of NIMH is geared to the broadest possible scientific coverage of clinically relevant research. Each of the Institute's three major extramural divisions assumes responsibility for research on mental illness, while the task of translational research – that is, applying knowledge gained at each level of analysis to clinical and service system needs – is shared across NIMH. In practice, this means that the Division of Neuroscience and Basic Behavioral Science, which is the locus for strong molecular genetics and fundamental behavioral research, also administers an innovative program of translational research centers, wherein major universities receive support to foster collaboration among diverse disciplines and departments to examine a particular disorder, such as schizophrenia. In the Division of Services and Intervention Research, immediate treatment needs are being addressed through an unprecedented series of multi-year clinical effectiveness trials that focus on discrete clinical issues: adolescent depression, sequenced treatment for adult depression, the use of atypical anti-psychotic medications in schizophrenia and depression, and enhanced treatments for bipolar disorder. Yet another illustration of the

Institute's priority on improving clinical care is evident in a new Treatment Development Initiative that will foster collaboration among NIMH, the FDA, and the pharmaceutical industry with the aim of introducing fundamentally new approaches to the development of treatments for mental disorders. In the NIMH Intramural Research Program, a major new Mood and Anxiety Disorders research program has been established that has recruited senior investigators from academia and now stands at the leading edge of research aimed at understanding and measuring structural changes in the brain associated with depression, chronic stress, and post-traumatic stress disorder, and at developing brain-based biomarkers to be used in monitoring treatment progress and outcome. It is noteworthy, too, that NIMH has created a new program in dissemination of research to fund studies that seek to understand the best ways to ensure that quality services are provided to community populations.

In Fiscal Year 2001 NIMH spent $1,374,000 on Traumatic Brain Injury.

RESEARCH PRIORITIES AT NIMH

Mr. Istook: Dr. Nakamura, we know you are interested in reshaping research priorities within all of the NIH institutes (including NIMH) to better reflect public health needs. At NIMH, several recent Mental Health Advisory Council reports, have recommended improving the relevance of prevention research into early interventions, clinical research to actual practice, and of behavioral research to serious mental illnesses. Could you please discuss some of the difficulties you've encountered in continuing NIMH's efforts to insure research is done on the greatest public health needs?

Dr. Nakamura: NIMH has mounted many initiatives to speed the translation of basic research into treatment and prevention efforts for mental disorders and behavioral problems that present important public health burdens, such as schizophrenia, depression, borderline personality disorder, and youth antisocial behavior. While each area poses its own particular research challenges, certain issues at various steps of the translational process cut across them which NIH is working to address. For example, NIMH is supporting research to: 1) translate biological and behavioral risk factors into targeted interventions for exploratory studies; 2) provide more systematic testing of interventions identified in preliminary studies as promising for prevention or clinical practice; 3) benefit from better linkage to other agencies for large-scale community trials of interventions of proven worth in intermediate trials. In addition, intensive efforts are being supported to overcome several structural barriers that impede essential kinds of translational prevention research. These include: 1) fostering multidisciplinary research training to improve collaboration and communication across research fields, teams and departments; 2) encouraging the creation of multidisciplinary peer review panels that are receptive to new kinds of translational research; 3) providing incentives to academic institutions to promote essential long-term prevention studies, even though some studies may lag in producing publishable results. Finally, NIMH is increasing its efforts to disseminate well-established research findings to those who can best apply them to clinical care and prevention. For example, in the area of youth antisocial behavior, a

mature body of research information suggests a number of scientifically well-documented prevention approaches, but they are not yet well recognized or widely adopted. At the same time, other widespread prevention approaches have been demonstrated to be ineffective or harmful. NIMH is working to disseminate these research findings to multiple audiences, including: researchers, practitioners, federal and local policymakers, and law enforcement and justice personnel.

SUCCESS RATES

Mr. Istook: Where does NIMH stand relative to other NIH institutes on the rate of grants submitted and funded?

Dr. Nakamura: In FY 2001 the average success rate (awarded grants as a percentage of total grant applications) for research project grants was 32 percent NIH-wide. Success rates across the 23 NIH Institutes and Centers ranged from a high of 43 percent to a low of 17 percent. The NIMH ranked 14th from the highest with a success rate of 31 percent.

SCHIZOPHRENIA RESEARCH

Mr. Istook: Discuss the budget for the last 8 years on schizophrenia. Discuss advances in the field, if any, and promising areas of research.

Dr. Nakamura: The budget for schizophrenia research for the last eight years is as follows:

Total NIMH Spending for Schizophrenia	Total NIH Spending for Schizophrenia
FY 1994 Actual – $110,416,000	$113,147,000
FY 1995 Actual – $108,900,000	$112,016,000
FY 1996 Actual - $108,811,000	$111,479,000
FY 1997 Actual - $108,659,000	$110,868,000
FY 1998 Actual – $132,455,000	$135,356,000
FY 1999 Actual - $196,515,000	$200,562,000
FY 2000 Actual - $234,799,000	$240,966,000
FY 2001 Actual - $265,294,000	$276,068,000

We stand on the verge of a revolution in our understanding of schizophrenia and our ability to treat people who suffer from this devastating illness. Not so long ago, a diagnosis of schizophrenia was considered by many to be the psychiatric equivalent of a terminal illness. With the introduction, first of clozapine, then more recently, a whole series of "atypical" antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, and soon aripiprazole and iloperidone), entirely new vistas have opened in the pharmacotherapy of schizophrenia. A major National Institute of Mental Health

(NIMH) sponsored clinical trial (with sites in 34 different states) is comparing these new antipsychotics (Clinical Antipsychotic Trials of Intervention Effectiveness, CATIE), and will define how they should be used to treat schizophrenia. These new antipsychotics seem to allow patients, families, and their clinicians to focus on coping with illness, rather than just symptom control. It appears that, with appropriate pharmacotherapy and psychosocial rehabilitation, many people with schizophrenia may be able to lead productive, meaningful lives.

In addition in 2001, NIMH launched a 4-site 5-year clinical trial to study the effectiveness of 3 different antipsychotic medications for children and adolescents (8-19 year old) suffering from schizophrenia, schizophreniform disorder, or schizoaffective disorder. Both short- and long-term effects will be comprehensively assessed for up to 1 year of treatment. The study is conducted under a cooperative agreement at the University of North Carolina (Dr. Jeffrey Lieberman), University of Washington (Dr. Jon McClellan), Case Western University (Dr. Robert Findling), and Harvard University (Dr. Jean Frazier).

While illness management in schizophrenia is important, it is not a cure. Finding a cure will depend on understanding what has gone wrong in the brains of people with schizophrenia. Advances in basic neuroscience, and sequencing the human genome, as well as development of sophisticated neuroimaging techniques offer hope that the puzzle of schizophrenia will be solved. We have long known that schizophrenia can be inherited, but because multiple genes are involved, previous studies were too small to identify them. The NIMH has set out to gather a sufficiently large number of families with more than several members affected by schizophrenia to pin down the genes that predispose people to developing the illness. Once these are identified and with the new knowledge of the human genome, the function of certain genes in the brain can be learned and a whole new generation of specific treatments may become possible.

Through sophisticated new techniques to image brain function, we are increasingly able to understand the neural circuitry that underlies the symptoms of schizophrenia. With the development of methods to noninvasively stimulate selected regions of brain, it even may be possible to turn off some of the troubling hallucinations and delusions suffered by patients with schizophrenia.

Finally, over the past decade, it has become increasingly clear that schizophrenia can be a disorder of brain development. Some subtle alteration in neuronal migration or connectivity as the brain develops later may become expressed as schizophrenia. In other words, since the "abnormality" that causes schizophrenia may be present well before a person develops overt psychosis, something must happen to trigger onset of the illness. If this is the case, then it may be possible to identify young people at risk for psychosis before active symptoms disrupt social, academic and vocational functioning. NIMH is developing methods to identify individuals in the earliest stages of schizophrenia, trying to prevent chronic disability through early intervention, and hoping

that this will eventually lead to treatments that can actually prevent onset of illness. While this prospect is exciting, there are also many ethical dilemmas that must be confronted before any such attempts at primary prevention can be made.

While schizophrenia remains the most disabling of all mental disorders, over the last eight years, our ability to manage the illness and improve outcomes and our understanding of its basic biology have improved dramatically.

ACCESSING THE NEWEST ADVANCED TREATMENTS

Mr. Istook: In the last decade, many new treatments and services have been developed and proven for severe mental illnesses such as schizophrenia. What efforts are underway (or ongoing) to ensure that the improved treatment interventions being developed now will be effectively disseminated to providers?

Is NIMH collaborating with SAMHSA and CMHS on these efforts?

Dr. Nakamura: The NIMH has a specific program in research on dissemination and implementation of new knowledge that supports grants to find ways to ensure that effective treatments are brought to community practice. Ongoing activities in this program include a new announcement calling for grant applications in this area; new funding mechanisms to promote this area (including one jointly issued with CMHS on Children's Services); and sponsorship of workshops and conferences to foster new research ideas in this area. An example is a recent research workshop focused on implementing evidence-based practices into the public mental health sector.

NIMH has collaborated with SAMHSA, especially CHMS, on issues related to improving the implementation of new treatment interventions. CMHS representatives were actively involved in recent workshops and discussions about joint funding of future projects. Other collaborative efforts are underway to foster new research opportunities and implementation strategies.

PROMISING TREATMENTS FOR DIABETES

Mrs. Northup: Can you please update us on where you are with diabetes research. Specifically, where do you believe the most promising treatments lie?

Dr. Spiegel: Diabetes research is highly productive–continuously generating impressive findings and revealing new scientific opportunities. The vigor of diabetes research is evidenced in the many advances and opportunities recently identified by outside experts for a report the NIDDK is preparing at the request of this Subcommittee. This report will highlight progress in the field since the publication of the five-year Strategic Plan of the Diabetes Research Working Group in 1999. We expect to deliver the update to Congress this summer.

Clearly, we are able to document extraordinary achievements in diabetes, which have, in turn, opened up new avenues of opportunity for exploitation. Let me give you just a few examples. With regard to treatments for type 2 diabetes, further elucidation of the basis for insulin resistance has provided novel targets for therapeutic intervention, which are currently being refined and tested. With regard to type 1 diabetes, the goal must be to cure the disease by providing a replacement for the destroyed islets, rather than by compensating for the loss of natural insulin-producing capacity through the administration of insulin. Recent, preliminary results with islet transplantation in adults with severe type 1 diabetes encourage us that cell replacement therapy could provide the cure we seek. However, major challenges remain, both in terms of the adequacy of the supply of insulin-secreting cells for transplantation, as well as in terms of preventing the recipient's immune system from attacking the transplanted cells.

STEM CELL RESEARCH

Mrs. Northup: Given the controversy surrounding stem cell research, where do you think the best opportunities for research are?

Dr. Kirschstein: Stem cells are an important discovery tool, and they have significant potential for development into therapies for a variety of diseases and conditions. This potential presents enormous opportunities for innovative research across a broad range of scientific disciplines. Embryonic and adult stem cells have distinguishing characteristics and properties that provide researchers with many options to explore key questions toward defining approaches to replace damaged or diseased cells and restore some of the human body's most critical functions. In plotting a time line for the course of discovery, it is encouraging to acknowledge the major advances that have come in just the past three years. For example, only recently have scientists discovered the ability of adult stem cells to grow into specialized cells and established the means to identify the key cells that are capable of doing so. In the past several months, investigators have presented the first evidence that mouse embryonic stem cells can restore function in animal models of immune deficiency and of Parkinson's disease.

To achieve the goal of developing cell-based therapies, the best opportunity for research is broadly represented by coupling the vast knowledge base in fields such as cell biology, genetics, and immunology with powerful research tools including databases and animal models. For example, during the next several years, it will be important to take the research to a higher level of ability to define the capability of embryonic and adult stem cells to proliferate, differentiate, survive, function, and avoid immune rejection. It is difficult to forecast at this early stage which of the stem cells or which methods for manipulating the cells will best meet the needs of basic research and clinical applications.

Currently, researchers are identifying the critical genes and proteins that provide stem cells with signals that guide their replication while in an unspecialized state. This also will provide important clues as to the way that these cells become neurons, muscle cells, or cells that produce insulin. Such information is necessary, for example, to understand how adult stem cells can be programmed to become replacement cells in a specific tissue. Given the resources such as the fully sequenced human genome, and protein databases and various growth factors, this area of stem cell biology will likely move quickly. Using similar approaches, researchers have made the development of new 'markers' to identify adult stem cells and partially specialized cells a priority. For stem cell-based therapies to be used effectively, a unique population of cells will need to be used and at the present time the identifying 'markers' that distinguish cells that will become neurons from those destined to become blood cells are too simplistic to be used in guiding specialization of cells for therapeutic purposes.

As science proceeds down the path of developing cells for clinical applications, researchers also will take on major explorations of the immune system. Researchers will be trying to answer key questions about how the stem cell develops features that influence the acceptance or rejection of these cells by recipients. Other major areas to be approached in the next several years include the use of animal models of disease to study how stem cells can be directed to locate in particular organs or tissues, i.e brain, and how to regulate their growth and function. New bioengineering approaches are underway to refine the growth media used for conditioning stem cells and to create biomaterials that serve as scaffolds for growing cells into tissues such as muscle, kidney, and liver.

Based on advances in other species, researchers will undoubtably make rapid discoveries in some areas and uncover new roadblocks in others. A key to making the science move as quickly as possible will be the harnessing of knowledge and basic technologies from other fields of study. Another philosophical approach that NIH takes in expanding new fields of discovery is to bring new talents and skills from other areas of biology. NIH has already taken the first steps to broaden the research base through infrastructure awards and training initiatives with the goal of having many scientists do stem cell research. In addition, a wide array of program announcements and requests for proposals are signaling to the research community NIH's major commitment to advancing stem cell biology.

The trajectory at which discoveries are made will likely follow the path taken after many of the breakthroughs that have occurred over the years. It seems likely that there will be a major thrust forward in some areas and new obstacles reached and solved in others. While the assurances that stem cells will be successful in treating human conditions such as diabetes, Parkinson's disease, congestive heart failure, and spinal cord injury are likely to be many years away, NIH is ensuring that the first steps are being taken expeditiously through an intense focus on basic research.

RESULTS FROM STEM CELL RESEARCH

Mrs. Northup: When do you think we will see results from research done on stem cells (either adult or embryonic)?

Dr. Kirschstein: Some of the major accomplishments in stem cell science are likely to come in the areas of cell biology and genetics by which we learn the critical steps that regulate the specialization of cells. Large scale approaches to unraveling the genes that are activated or repressed and the biochemical communication networks within these unique cells will provide researchers with the means to more tightly regulate the specialization of cells and how to maintain their potential to replicate. For example, researchers will use animal models to replace cells or restore function in diseased tissues. Regulating these intricate mechanisms to activate a specific population of cells or directing the relocation of replacement cells to the proper tissues will be a major scientific advance. To this point, there have been very few studies that actually show the capability of stem cells to restore function, although they show enormous promise to do so. Studies of gene activation in human embryonic stem cells, with their unprecedented capability to develop into almost any tissue, may provide insights into cell division and into new approaches for treating cancer and immune disorders, as well as providing a new means for providing replacement genes in dysfunctional tissues. Scientists will begin to understand the "acceptance" of these cells by the immune system as the earliest foundations for transplantation therapies are laid down. Major advances in cellular engineering will enable many types of specialty cells to be grown in culture conditions using matrix scaffolds to support the future development of new tissues and organs for transplantation. Overall, the first steps in this emerging new scientific field will come from basic science. These basic steps will build the knowledge and technologies needed to bring adult and embryonic stem cells to clinical studies in treating human disease.

STEM CELL RESEARCH PROJECTS

Mrs. Northup: How many different research projects involving stem cell research including those NOT done by NIH are being conducted in the United States?

Dr. Kirschstein: It is difficult to capture the breadth of this rapidly emerging field particularly with regard to the number of privately sponsored research projects. We do know, however, that across the biomedical research enterprise, there is growing

investigator interest in stem cell research. For many years, NIH has funded research on stem cell biology in animal systems and adult human stem cells, predominantly hematopoietic (blood/bone marrow) stem cells, and these areas of investigation continue to grow. There is also an increase in research activity for human adult stem cell biology, because of the recent discovery that some cells are now able to take on the features of cells that differ from the tissue of their origin. NIH has recently started funding research with human embryonic stem cells. Therefore, any research that has been done in this area to this point has been conducted with non-Federal means of support.

GLUCOSE SENSORS RESEARCH

Mrs. Northup: What is the latest research showing about glucose sensors?

Dr. Spiegel: One of the greatest improvements in the management of both type 1 and type 2 diabetes in the past two decades has been the introduction and widespread implementation of reliable, accurate self-glucose monitoring devices. These devices have made possible improved control of blood sugar which has been shown to dramatically reduce the risk of diabetes complications. Nonetheless, the pain associated with finger sticks to obtain blood for glucose monitoring and the need for multiple daily measurements is one of the most burdensome aspects of diabetes management. Also, for many patients periodic measurements, several times daily, do not provide sufficient information to achieve the recommended levels of control and avoid low blood sugar reactions. Ideally, we would like to see development of a pain-free device capable of continuously monitoring blood glucose. Such a device, if combined with an insulin delivery system calibrated to deliver insulin in response to blood glucose measurements, would constitute a so-called "closed loop" system, totally independent of the need for manipulation by the patient.

Several types of technology are under development. Noninvasive technologies, which can measure glucose levels without penetrating the skin, are being explored but so far obtaining results has proven difficult. Other techniques have been developed to measure glucose in the interstitial fluid under the skin. Glucose in the interstitial fluid generally correlates well with the blood glucose. Significant progress has been made with systems that extract interstitial fluid and analyze glucose in the collected fluid. Progress has been also made in the development of enzymatic glucose sensors in several forms: intravenous implants; needle-like probes penetrating the skin with the sensor tip in the tissues just below the skin; or devices fully implanted underneath the skin. Researchers have implanted such devices in an animal model of diabetes, with promising results. Investigators feel that this technology can be further optimized by using microcircuitry, which would miniaturize the sensor to approximately the size of a large jelly bean, implantable in an outpatient setting with local anaesthesia.

The NIDDK has provided significant support for sensor development and other efforts are supported by industry. We are currently soliciting applications for projects using state-of-the-art bioengineering approaches to develop new approaches for glucose

sensing and improved glucose sensors. A second initiative, in collaboration with the National Institute of Child Health and Human Development, is supporting clinical studies to evaluate usefulness of currently available continuous glucose sensors in improving glucose control and avoiding hypoglycemia or low blood sugar.

COMMERCIALLY AVAILABLE GLUCOSE SENSORS

Mrs. Northup: Is there any sense when something like a glucose sensor would be commercially available?

Dr. Spiegel: Some glucose sensors are already commercially available; however, none of them yet provides the type of precise, continuous and "real-time" sensing of glucose that is performed by the specialized cells in the body that make insulin. Therefore, research is continuing to refine and extend the availability of glucose sensors. Let me highlight the development and current status of the field.

Meters for self-monitoring of blood glucose became available in the 1970s and revolutionized the management of diabetes. At that time, the meters required several drops of blood from a fingerstick. Advances in technology then led to the development of improved meters requiring very little blood, allowing testing to be done on the upper arm, forearm or thigh where pricking the skin is less painful. However, these meters can only provide the measurement of the blood glucose at the time of the sample and miss many of the high and low blood glucose levels that typically occur throughout the day and night. Two continuous glucose monitoring systems have now been approved by the FDA.

One continuous glucose monitoring system, developed by Medtronic MiniMed, is comprised of a tiny sensor inserted under the skin of the abdomen, which is connected to a pager-like device worn on the belt which collects the data. The pager can be downloaded and transmits the data to a personal computer. Usually the patient wears the glucose sensor for up to 72 hours. Until more experience is obtained with this sensor, it is only approved for use under supervision of a physician. The blood glucose measurements are transmitted to a physician who reviews them and makes suggestions about improving the patient's diabetes management.

Another device was approved by the Food and Drug Administration in March 2001. It is the GlucoWatch Biographer, manufactured by Cygnus Inc., which was approved to detect trends in glucose levels in adults age 18 and over with diabetes. It must be used along with conventional blood glucose monitoring. The device, which looks like a wristwatch, pulls body fluid from the skin using small electric currents and checks blood glucose levels every 20 minutes. The GlucoWatch Biographer is currently available only in the United Kingdom. It is expected that it will be available in the U.S. in 2002.

These devices could not have been developed without the support of NIDDK for basic and clinical research in diabetes. The NIDDK is continuing to support research in non-invasive glucose monitoring and other approaches that may result in improved treatment for diabetes. A particular imperative for this research was the findings from the NIDDK's Diabetes Control and Complications Trial, which showed that the eye, kidney and nerve complications of diabetes could be dramatically prevented or delayed by maintaining blood glucose levels as close to normal as possible throughout the day. Unfortunately, we still have not developed simple and fully effective treatments which allow patients to achieve tight glucose control so that they can reap these benefits. With current treatments, the risk of dangerous episodes of low blood glucose limits our ability to achieve near normal glucose control. For all these reasons, we continue to support a strong multi-faceted research program aimed at optimizing glucose control, while, at the same time, developing strategies for preventing the destruction of insulin-producing islets and for restoring normal beta cell function.

DIFFERENCE BETWEEN TYPE 1 AND TYPE 2 DIABETES RESEARCH

Mrs. Northup: There are many more people who have type 2 diabetes than type 1. How is the research for type 2 different, especially given that type 2 can be prevented?

Dr. Spiegel: Unlike type 1 diabetes–in which the immune system destroys the insulin-producing islets so that there is insulin deficiency–in type 2 diabetes, the body is resistant to the action of insulin. Initially, the islets compensate by secreting more insulin, but type 2 diabetes develops because the islets eventually fail. Research on type 2 diabetes therefore focuses on the basis for insulin resistance and what can be done to reverse it, as well as on the basis for the failure of the islets to secrete adequate amounts of insulin. Indeed, research on type 2 diabetes to date set the stage for our Diabetes Prevention Program (DPP) multi-center trial showing that modest reduction in weight and increased exercise can prevent or delay the onset of type 2 diabetes in high risk groups–indicative of improved insulin sensitivity and preserved islet function in these individuals.

RESOURCES FOR TYPE 1 DIABETES VS. TYPE 2 DIABETES

Mrs. Northup: Is there any way to determine how much money has been spent on type 1 diabetes compared to type 2?

Dr. Spiegel: Some of the diabetes research NIH supports is focused explicitly on type 1 diabetes, including studies of the autoimmune and genetic basis of the disease, clinical trials to prevent type 1 diabetes, and studies of islet transplantation. Other studies, such as research on the mechanisms of insulin resistance, and approaches to prevent or reverse it, are directed at type 2 diabetes. However, a substantial amount of research has relevance to both type 1 and type 2 diabetes and cannot be subdivided in a scientifically meaningful way. For example, the eye, kidney and nerve complications

have a similar pathogenesis in both type 1 and type 2 diabetes and research on prevention and treatment of complications is therefore applicable to both forms of diabetes. Additionally, failure of the insulin-producing beta cells is central to both type 1 and type 2 diabetes and so research to understand, at the molecular level, these critically important cells is relevant to both forms of diabetes. Our diabetes research infrastructure support, such as diabetes centers, and our support for training new investigators also enhances research on both forms of diabetes. Hence, it is not really possible to divide total NIH spending on diabetes into type 1 diabetes versus type 2 diabetes.

STROKE PREVENTION

Mrs. Northup: What has the research shown regarding behavior patterns that could be modified to reduce the chances of stroke?

Dr. Penn: Although there are several risk factors for stroke that cannot be controlled, such as age, family health history, race and gender, we know that there are lifestyle changes individuals can undertake to reduce the chance of having a stroke.

High blood pressure is the most important risk factor for stroke. In fact, stroke risk varies directly with blood pressure. It is widely believed that the effective treatment of high blood pressure is a key reason for the accelerated decline in the death rates for stroke. However, a large proportion of people with high blood pressure are still unaware that they have this disorder. Diabetes mellitus is an independent risk factor for stroke, and is strongly correlated with high blood pressure. People with diabetes often have high cholesterol and may be overweight, increasing their chances for a stroke even more. Recent studies have shown that in men, overweight and obesity increase the risk for not only coronary heart disease, but for stroke also.

Cigarette smoking has been shown to be another significant risk factor for stroke. Moreover, the use of oral contraceptives combined with smoking greatly increases stroke risk.

A number of studies have shown that lifestyle interventions can reduce the chance for a first stroke. These changes include quitting smoking, increasing the level of aerobic physical activity, maintaining a healthy weight, limiting the consumption of alcohol to moderate levels for those who drink, reducing salt and sodium intake, and eating a reduced fat diet high in fruits, vegetables, and low-fat dairy food. Additionally, we continue to encourage people to have their blood pressure, cholesterol and blood sugar levels checked and if needed, take action to control them.

ALS RESEARCH

Mrs. Northup: What is the current research showing about the best opportunities for prevention and treatment for ALS (or Lou Gehrig's disease)?

Dr. Penn: For ALS, probably the most important point to emphasize is not any single lead, but the convergence of several different areas of research on this disease. It is remarkable that virtually all of the major themes in neurodegeneration seem to be relevant to understanding this disease. We support a very active program of research on ALS, including investigations into the role of genetics, glutamate excitotoxicity, calcium, free radicals, mitochondria, trophic factors, "cell suicide," and the nerve cells' cytoskeleton, or internal supporting structure. In addition, we support broad, cross-cutting activities with implications for treating ALS, such as research on stem cells, drug development, and gene therapy. Our program ranges from studies at the molecular level to clinical trials. This year we funded several new grants from a request for applications focused on ALS and related diseases, which resulted from a workshop held the previous year. In cooperation with the ALS Association and other groups, we also began new efforts this year to screen drugs for ALS. We will continue to look at ALS from many perspectives, until the various lines of research come together–as they increasingly seem to be doing–and we develop a way to prevent or cure the disease.

Mrs. Northup: Is the research specifically focused on the rapid progression of this disease?

Dr. Penn: Many researchers are certainly focusing on why most cases of ALS progress so rapidly, compared with other neurodegenerative disorders such as Alzheimer's and Parkinson's. Other key and closely intertwined questions include what triggers the disease in the first place, and why only certain nerve cells–the motor neurons that activate muscles–are vulnerable. Several years ago scientists discovered a defective gene that causes a type of inherited ALS. This finding was a boon to research because the gene provided clues about what goes wrong in ALS, and it led to the development of a mouse model of the disease, allowing experiments designed to understand these key questions and to test treatments. This year, scientists developed a rat model of ALS, which should be valuable for studies that are difficult or impossible in mice, and other researchers discovered the gene for another form of inherited ALS, which should lead to further insights into discovering how this disease is triggered and why it progresses so rapidly.

CANCER RESEARCH FUNDING

Mrs. Northup: The President has proposed a dramatic increase in cancer-related research funding. How do you plan on administering that funding and providing proper oversight of grantees?

Dr. von Eschenbach: As the number of NCI's research initiatives has grown in recent years, so too have the responsibilities of our scientific managers and administrators. The Research Management and Support budget is the primary funding directed toward the critical oversight of NCI programs. Included are the central administration functions, overall program direction, grant and contract review and administration, personnel, program coordination, and financial management. NCI has

been diligent in exercising care to keep these costs to only those essential for proper stewardship of the Federal funds provided. NCI research management costs have remained relatively stable and in FY 2001 were less than 4% of our total budget. We do anticipate a proportionate need for growth of NCI program officials for potential oversight of and guidance to recipients of NCI research funds. There are more sophisticated research protocols and research initiatives that call for increased collaboration with NCI grantees and subsequent oversight. In areas of basic science as well, more and more projects involve direct NCI staff efforts to manage national consortia of awardees through cooperative agreements.

The NCI extramural program managers, which are funded from the Research Management Support budget, have prime responsibility for the monitoring of individual grants within their research portfolios. These managers must stay current in their area of scientific expertise and must develop a relationship with their grantees in order to be able to evaluate progress. The managers also think in terms of how their grantees' research fits into the broader picture of the NCI research agenda.

From FY 1997 to FY 2001, dollars obligated for grant awards increased by more than 60%, and the number of grant related actions increased by 33%. We have begun to see management benefits from the increased electronic transmission of information and improved automated tracking and monitoring systems for data exchange.

To ensure wise use of resources to meet the goals of the NCI, we seek out expert advice on operational and administrative policies from both within and outside the Institute. Examples of these groups include the National Cancer Advisory Board (NCAB), the Board of Scientific Councilors, the Board of Scientific Advisors, and the NCI Executive Committee.

TRENDS REGARDING CANCER

Mrs. Northup: What sort of trends are you seeing regarding incidences of cancer, not only in terms of total number of diagnoses, but in different types of cancer? Are these trends, either increases or decreases, recognizable across geographic areas?

Dr. von Eschenbach: Based on data collected by NCI's Survival, Epidemiology and End Results (SEER) program, the rate of new cancer cases for the most recent period is stabilizing and, based on data collected by CDC's National Center for Health Statistics, the rate of cancer deaths is falling overall. Some behaviors that play a role in cancer risk have also shown improvement. For example, adult smoking is down dramatically since the 1960s, although rates only fell slightly in the 1990s. Alcohol and fat consumption is headed down, and vegetable consumption is up. The use of screening tests for breast and cervical cancers is increasing. Screening for colorectal cancer is also increasing; however, it still remains low.

Despite these signs of progress, there are some cancers that are rising dramatically, such as cancer of the esophagus and melanoma skin cancer. Lung cancer in women continues to rise, but not as rapidly as in the past. Youth smoking has been on the rise, though data show there may be a recent, promising decline. People are doing less to protect themselves from the sun. More people are overweight and obese, and physical activity is increasing only slightly. Unexplained cancer-related health disparities remain among population subgroups. For example, African-Americans and people with low socioeconomic status have the highest overall rates for both new cancers and deaths.

The NCI Surveillance, Epidemiology, and End Results (SEER) Program collects incidence data on eleven geographic areas of the United States. SEER collects and publishes cancer incidence and survival data from 11 population-based cancer registries and three supplemental registries covering approximately 14 percent of the U.S. population. In addition, the SEER program is the only comprehensive source of population-based information in the U.S. that includes stage of cancer at the time of diagnosis and survival rates within each stage. The cancer incidence rates and trends for the latest period (1992 to 1999) vary by geographic area and cancer site. The overall cancer incidence rate decreased 0.9 percent per year during this period. Atlanta, San Jose-Monterey, Los Angeles and San Francisco showed the largest decreases, while most of the other areas were relatively flat.

Complementing the SEER program is the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries (NPCR). This population-based system for monitoring cancer, which began in 1994, currently supports central registries in 45 states, the District of Columbia, and three territories. Ninety-six percent of the U.S. population is covered by this system. The NPCR enables reporting of cancer data by age, sex, race/ethnicity, and geographic area--within a state, between states, and between regions. Data about cancer incidence, stage at diagnosis, and first course of treatment provide information for evaluating progress toward cancer prevention and control--at the local, state, and national levels. Statewide cancer data are used to determine cancer patterns among various populations; monitor cancer trends; guide planning and evaluation of cancer control programs; help set priorities for allocating health resources; and advance clinical, epidemiologic, and health services research. In addition, this data will allow for the future review and analysis of local patterns of disease.

For cancer mortality trends, the data are from the National Center for Health Statistics' public-use file and cover the entire United States. The death rates and trends vary by cancer site and state.

In addition, NCI's recently published Atlas of cancer mortality in the United States, 1950-94, includes more than 250 computerized color-coded maps showing geographic variations in cancer mortality rates during 1970-94 and compares them with

corresponding maps for 1950-69. The web site for the Atlas is http://www3.cancer.gov/atlasplus/. Recent rates and trends, 1992 through 1999, are presented by geographic area for cancer incidence and mortality in the attached tables.

Table 3
Cancer incidence rates and trends, by SEER geographic area, 1992-1999.

	All sites Rate	Colon - rectum Rate	Lung Rate	Female breast Rate	Prostate - male Rate	All sites Trend	Colon - rectum Trend	Lung Trend	Female breast Trend	Prostate - male Trend
Eleven SEER registries	475.7	54.2	63.9	132.1	179.0	-0.9*	-0.6	-1.3*	1.1*	-4.2*
San Francisco-Oakland SMSA	480.9	53.9	63.2	138.4	171.5	-1.4*	-1.2	-2.2*	1.3*	-3.6*
Connecticut	510.2	61.0	70.2	143.5	174.5	-0.1	0.0	0.0	1.2*	-3.1*
Detroit (Metropolitan)	526.3	58.4	80.8	130.8	225.7	-0.9	-0.8	-1.1*	0.2	-4.4*
Hawaii	428.2	55 0	53.9	125.0	136 8	-0.4	-0.5	-0.4	3.2*	-4.7*
Iowa	477.7	63.8	67.9	130.0	166.1	-0.5	0.4	-0.6	0.6	-4.9*
New Mexico	417.0	43.2	49.1	117.7	162.3	-1.0	-0.1	-0.6	1.1	-5.3*
Seattle (Puget Sound)	500.3	52.8	72.9	145.3	174.4	0.2	-0.4	0.0	2.2*	-2.2
Utah	404.1	42.4	32.0	115.0	191.2	-0.6	0.2	-0.6	1.4*	-5.2
Atlanta (Metropolitan)	497.3	53.6	73.9	137.8	213.8	-1.8*	-2.2*	-1.4*	1.0*	-6.5*
San Jose-Monterey	454.5	50.0	56.4	137 2	163.0	-1.1*	-1.9*	-2 2*	1.2	-3.0
Los Angeles	450.5	50.5	56.7	122.9	172.1	-1.4*	-0.6	-2.3*	0.7*	-4.8*

Rates are per 100,000 and age-adjusted to the 2000 U.S. standard.

* Trend 1992-1999 is significant.

Table 4
Cancer death rates and trends, by State, 1992-1999.

	All sites Rate	Colon - rectum Rate	Lung Rate	Breast - F Rate	Prostate - M Rate	All sites Trend	Colon - rectum Trend	Lung Trend	Breast - Female Trend	Prostate Trend
Total U.S.	208.7	22.3	58.2	29.7	35.7	-0.9*	-1.7*	-0.7*	-2.4*	-3.5*
Alabama	220.2	19.9	63.8	27.3	41.9	-0.4*	0.0	0.1	-1.7*	-0.6
Alaska	203.8	22.2	60.4	26.2	27.4	-2.1*	-5.4	-2.8*	-5.0*	-10.4*
Arizona	190 9	19.1	52.8	26.9	31.4	-1.1*	-1.5*	-1.0*	-1.7	-4.4*
Arkansas	221.5	21.9	72.0	27.3	38.5	-0.6*	-1.5	-0.8*	-1.8*	-2.3*
California	191.1	19.3	50 7	28.2	31.5	-1.5*	-2.5*	-1.7*	-2 6*	-4.6*
Colorado	177.1	19.1	42.2	25.5	33.4	-0.9*	-2.0*	-1.1	-2.6*	-4 9*
Connecticut	201.8	21.9	52.3	30.2	32.4	-1 0*	-2.4*	-0.4	-1.8*	-3.6*
Delaware	236.9	24.6	69 7	33.5	41 0	-0.9*	-1.2	-0.3	-2.4	-4.8
Washington, DC	253.2	26.1	60.6	39.2	58.4	-1.8*	-1 4	-1.6	-0.4	-4.1
Florida	203.6	20.9	60.3	28.4	31.8	-0.9*	-1.8*	-0 7*	-2.7*	-4.1*
Georgia	214.0	20 0	63.3	28 7	44.0	-0 7*	-1.7*	-0.4	-1.1	-3.4*
Hawaii	164.0	17.3	40.6	20.6	23.6	-1.2*	-4.4*	-0.2	-1.0	-4.0
Idaho	185.3	18.9	45.9	27.1	37.2	-0.2	0.5	-0.2	-0.6	-4 2*
Illinois	216.2	24.4	58.9	32.1	36.4	-1.0*	-2.2*	-0.7*	-2.3*	-2.7*
Indiana	218.9	24.3	65.4	30.0	36.6	-0.2	-1.1*	0.3	-2.2*	-1.4*
Iowa	196.5	23.5	53.4	28.9	34.8	-0.9*	-1.4	-0.6	-2.8*	-2.5*
Kansas	194.3	20.8	54.4	27.4	33.3	-0.6	-1.2	0.4	-2.2	-3.6*
Kentucky	233.2	24.6	78.4	29.1	36.0	-0.6*	-1.9*	-0 5	-2.1*	-2.1*
Louisiana	238.0	24.3	70.1	31.3	43.2	-0.4	-0.3	-1.0	-1.4*	-2.3*
Maine	227.9	25.4	65.4	29.7	35.5	-1.0*	-2.0*	-0 9	-2.3*	-4.9*
Maryland	225.0	25.2	63.1	32.2	40.6	-1.4*	-2.4*	-0.9*	-2.1*	-4.2*
Massachusetts	216.9	25.0	57.2	32.2	34.9	-1.4*	-2.7*	-0.9*	-3.8*	-3.3*
Michigan	210.8	22.5	59.3	30.3	36.7	-1.1*	-1.8*	-1.1*	-2.3*	-4.0*
Minnesota	193.7	20.5	47.5	28 6	36.5	-0.7*	-1.6	0.1	-2.6*	-2.8*
Mississippi	226.3	21.1	68.3	28.4	46.8	0.4	0.6	1.5*	-0.2	-1 2
Missouri	215.1	23.1	65.3	28.8	34.0	-0.5*	-1.3	-0.2	-1 5	-3.7*
Montana	198.4	20.1	52.7	27.7	38.7	-0.8*	-2.6	0.9	-4.7*	-4.0*
Nebraska	190.6	22.9	50.9	28.3	30.8	-0 5	-0.6	0.1	-3.1*	-3.5*
Nevada	224.3	23.2	68.5	29.2	34.9	-1.2*	0.1	-0.4	-2.7*	-4.4*
New Hampshire	222.4	25.2	61.1	32.1	34.1	-1.0*	-1.9*	-0 5	-3.8*	-4.4*

New Jersey	220.3	25.7	56.3	33.4	36.2	-1.2*	-2.8*	-0.8*	-2.6*	-4.2*
New Mexico	183.3	18.6	41.7	27.1	35.0	-0.7*	-1.0	-0.3	-2.4	-2.3
New York	206.5	24.3	52.6	32 7	34.0	-1.4*	-2.3*	-1.3*	-2 9*	-3.8*
North Carolina	214.0	21 6	63.1	29.4	42 1	-0.6*	-1.6*	-0.1	-1.9*	-3.5*
North Dakota	191.3	21.9	45.3	28.6	39.1	-0.8*	-2.1	-0.2	-2.9*	-5.5*
Ohio	220.4	24.8	63.3	31.7	36.4	-0.7*	-1.2*	-0.6*	-2.3*	-3.5*
Oklahoma	209.0	21.1	65.9	28.3	33.1	-0.3	-0.4	-0.2	-1.6	-3.7*
Oregon	205.0	20.0	59.4	28.3	35.7	-0.7*	-0.6	-1.2*	-1.6*	-2.0*
Pennsylvania	217.3	25.3	57.7	32.3	36.1	-0.8*	-1.8*	-0.4	-2.8*	-3.0*
Rhode Island	219 9	24.9	62.5	32.2	34.5	-0.5	-2.0	0.2	-3.2*	-1.2
South Carolina	217.1	22.2	61.4	29.0	45.5	-0.5*	-1.5	-0 1	-1.2	-3.2*
South Dakota	195.9	23.1	49.9	27.6	36.8	-0.3	-0.3	-0.4	-5.8*	-4.0*
Tennessee	222.9	22.3	70.0	29.5	38.0	-0.1	-1.5	0.1	-2.2*	-1.9*
Texas	206.3	21.1	59.6	27.7	36.0	-1.2*	-1 3*	-1.2*	-2.4*	-3.3*
Utah	154.5	16.8	25.8	25.0	37.7	-0.2	-1.1	-0.2	-1.5	-2.7*
Vermont	214.3	24.3	58.4	29.6	37.8	-0.4	1.3	-0.5	-2 6*	-4.4
Virginia	216.9	22.6	62.3	30.4	40 9	-0.7*	-1.5	-0.5*	-2.1*	-3.0*
Washington	201.2	19.7	57.6	28.0	32.9	-0 8*	-1.7*	-0.5	-3.0*	-4.6*
West Virginia	227.3	24.1	72.3	28.1	33.8	-0.4*	-0.5	0 4	-1.3	-3.3*
Wisconsin	201.8	21.9	49.9	29.2	38.0	-0.5*	-1.2*	0.3	-2.7*	-4.0*
Wyoming	196.3	21.7	50.5	28.2	39.5	0.1	2.6	-0.3	-2 9*	-4.4

Underlying mortality data provided by NCHS (http://www.cdc.gov/nchs)

Rates are per 100,000 and age-adjusted to the 2000 U S. standard.

Percent changes were calculated using 1 year for each end point; EAPCs were calculated using weighted least squares method.

* Trend 1992-1999 is significant.

IMPACT OF ANTHRAX OUTBREAKS ON RESEARCH

Mrs. Northup: How have the anthrax outbreaks from last fall changed the direction of research being conducted on this disease?

Dr. Fauci: NIAID supports a research program on anthrax that includes the development of therapeutics, vaccines and diagnostics. While the anthrax outbreaks of last fall have not changed the direction of this research program, they certainly have accelerated its pace. In December of 2001, NIAID announced several new research initiatives targeted at the CDC Category A agents of bioterrorism, including anthrax. The response to these initiatives has been very strong and the scientifically meritorious applications will be funded before the end of fiscal year 2002. NIAID is also leading a major DHHS initiative to develop and produce a new anthrax vaccine. In February of 2002, NIAID convened a Blue Ribbon Panel on Bioterrorism and its Implications for Biomedical Research to assess the current research on CDC Category A agents, identify goals for the highest priority research, and make recommendations on NIAID's role in achieving these priorities. Specific immediate and long-term research goals for anthrax were identified, these include: development, evaluation, and production of an anthrax vaccine; screening of existing FDA-approved antimicrobials and immunomodulators for efficacy against anthrax; encourage exploration of new targets for antimicrobial agents against anthrax; conduct comparative genomic sequencing of selected B. anthracis strains; develop robust, sensitive, and specific diagnostics for the detection of anthrax antigens in clinical specimens.

INFECTIOUS DISEASE RESEARCH

Mrs. Northup: Are there any infectious diseases where research has slowed over the past several years, but now is picking up due to the threat of bioterrorism?

Dr. Fauci: For the past decade, the NIAID has been gradually increasing its support for research into emerging infectious diseases, including those most likely to be used as agents of bioterrorism. Many of the organisms that pose the most serious bioterrorist threats are also naturally occurring diseases that cause significant public health problems in other parts of the world. Some of the bioterrorism agents that NIAID is focusing on are on CDC "Category A" list such as antrhax, smallpox, and ebola, among others. Thus, a positive benefit of this past decade of research support in the area of emerging infectious diseases has been increased knowledge of many of the agents now considered bioterrorist threats.

COLLABORATIVE RESEARCH

Mrs. Northup: Does the NIAID collaborate or look to the research being done in other countries to learn of promising treatments or vaccines for diseases we are not so familiar with?

Dr. Fauci: NIAID has had a longstanding interest in, and commitment to, international collaborative research on endemic diseases affecting populations in foreign countries. This commitment is reflected in a variety of NIAID-supported collaborative research programs that are designed to lead to or result in prevention, amelioration, and/or treatment of infectious diseases with which the American public has less familiarity, and thus improve the health and quality of life of individuals in endemic areas while contributing to the development of US based medical interventions. Additionally, many diseases that are rated high on the list of potential bioterrorism agents are prevalent in international settings

One such long-standing program is the International Collaborations in Infectious Diseases Research (ICIDR) program, which is over 30 years old and currently involves 18 projects in 24 countries. Other examples include the two key HIV/AIDS initiatives, HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN). The HVTN is a network of clinical sites in the United States and abroad that is dedicated to the development of an HIV vaccine through testing and evaluating candidate vaccines in clinical trials. This network includes 18 sites in the United States and 11 international sites, including sites in Africa, Asia, South America, and the Caribbean. In an effort to reduce the worldwide spread of HIV, NIH created the HPTN, a global network of clinical trial sites that explores non-vaccine prevention strategies to reduce HIV transmission. The HPTN has nine sites in the United States and 16 sites overseas in Africa, Asia, Europe and South America. Because HIV is transmitted via different routes in different populations, developing a variety of HIV prevention strategies will have a significant impact on reducing transmission rates and slowing the spread of HIV worldwide.

In addition, we are working with Indian scientists who have a strong interest in developing a vaccine against rotavirus, a major cause of diarrhea and infant mortality in the developing world. We are also involved in collaborations with a number of overseas countries to identify natural products with therapeutic potential. These and more recent initiatives are outlined in the NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis, which was published in May 2001. True collaborative relationships between foreign scientists and US scientists are the foundation of the NIAID Global Health Program.

IMMUNE-BASED STRATEGIES

Mrs. Northup: What can you tell us about your immune-based strategies for preventing Alzheimers?

Dr. Hodes: One promising finding of recent basic research efforts was the ability of an immunization strategy to prevent or reverse formation of amyloid plaques in mouse models of Alzheimer's Disease (AD). The initial clinical trial of this AD vaccine approach, was conducted by the Irish pharmaceutical company Elan Corporation, plc and was not an NIH-funded trial. It was halted earlier this year when a number of

participants on the experimental treatment experienced deleterious brain inflammation. Despite the unfortunate outcome of this trial, the science on which the study was based may still lead to development of better and safer strategies for arresting or reversing the brain lesions of AD. In collaboration with the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA) has already issued a Request for Applications (RFA) and funded a number of studies to better understand the science underlying the vaccine approach. These include studies characterizing behavior improvements in mice treated with the vaccine, several characterizing the pertinent aspects of the multi-faceted immune responses that help remove amyloid from the brain, and one investigating whether amyloid antibodies in the blood can draw amyloid out of the brain. Other scientists believe, on the basis of studies on human populations, that anti-inflammatory drugs can reduce the risk of developing AD, and animal studies also show that some anti-inflammatory drugs reduce plaque levels in mouse brain. At the same time as NIH –funded studies are continuing in test tube and animals, the NIA has funded a large prevention trial to see whether either of two anti-inflammatory agents will prevent or delay development of AD in cognitively normal older people.

BIOTERRORISM

Mrs. Northup: The NIH Budget request includes an increase of nearly $1.5 billion in 2003 for support of new research into bioterrorism agents and vaccines to fight them. The request includes funding for expanded research infrastructure to deal with the potential threats. What is the current capacity of the biomedical research community to address the impending threats? If this funding is intended to build adequate infrastructure, is it still in practicality, 18 months to two years away. What are we currently doing to insure an adequate response to protect the public from this threat?

Dr. Fauci: There is enormous capacity in the research and development community to respond to the needs for research in all areas related to countering potential bioterrorism agents and emerging infections. However, this requires that we expand vitally important research infrastructure capabilities to do research on the biological agents most likely to be used for these purposes. The existing facilities in the U.S. are limited in number. Lack of access to these specialized resources is the most critical limiting factor to conduct research on these dangerous pathogens. The most urgent infrastructure needs are provided for in the Budget, including: (1) specialized, high containment facilities in which research where animal testing of vaccine and drug candidates of the most dangerous pathogens can be conducted safely and effectively; (2) specialized animal models, including non-human primates, that will mimic the pathogenesis of the diseases in the human body; and (3) repositories that make vital research materials, such as diagnostic and therapeutic reagents, available to scientists.

The scientific community, throughout academia, industry, and federal agencies has rapidly responded with redirection of many research programs thereby increasing our research capability and capacity. While the actual building of the physical

infrastructure and other critical, specialized resources will take time, much other work which is not dependent on these specialized resources have begun but must be expanded. Several examples include: completed dilutional studies on the existing smallpox vaccine which showed that through dilution of the product we can safely increase the number of effective doses by five-fold, to 75 million doses; developing second generation smallpox and anthrax vaccines; starting Phase I trials later this year on Ebola, West Nile Virus, and third generation smallpox vaccine candidates; and screening of current drugs for their therapeutic affect on these types of diseases.

Also, there are substantial amounts of basic research that can be and will be done while these specialized resources are being developed. For instance, researchers can and will use attenuated, related or non-virulent strains of the targeted pathogens to conduct their preliminary research. However, for many scientists this type of research can only be carried so far before reaching a point where the work will stop unless the scientists have access to specialized, high-containment labs and specialized animal models to adequately test their concepts, theories and/or pre-clinical products, safely and effectively. Therefore, a key component of the NIAID strategic plan is to ensure that the critical, specialized resources become accessible to researchers in the next two to five years as the researchers start to need them.

BENEFITS BEYOND BIOTERRORISM

Mrs. Northup: As I understand it, without the associated public health threat, the agents likely to be used by Bioterrorists would fall into the category of Orphan Diseases. With all the funding invested in the issue of bioterrorism, are there long-term benefits to the health of the general public that can be expected from this investment, above and beyond protection against the immediate threat?

Dr. Fauci: In fact, many of the organisms in question, and a host of other emerging infectious diseases and drug-resistant microbes, already pose significant public health threats in many parts of the world. As we have seen many times, these same diseases can spread by natural routes and pose serious threats elsewhere. Thus, the positive long-term benefits for other diseases that will result from the large investment in both basic and translational research in biodefense will be substantial. Research on the microbial biology and pathogenesis of these organisms will enhance understanding of other more common and naturally occurring infectious diseases, both in the United States and around the world. Advancements in the arena of diagnostics, therapeutics, and vaccines will improve our ability to diagnose, treat, and prevent major killer-diseases, such as malaria, tuberculosis, HIV/AIDS, and a spectrum of emerging and reemerging diseases, benefitting people around the world. Basic research will greatly enhance our understanding of the molecular and cellular mechanisms of the innate immune system and its relationship to the adaptive immune system, and lead to improvements in the treatment and prevention of immune-mediated diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases. Finally, improved understanding of the mechanisms of regulation of the human immune

system will have positive spinoffs for diseases such as cancer, immune-mediated neurologic diseases, and allergic and hypersensitivity diseases, as well as for the prevention of rejection of organ transplantation.

PARKINSON'S DISEASE

Mrs. Northup: It is my understanding that part of the NIH strategy in researching Parkinson's disease is the development of 40 clinical centers to test neuroprotectants to slow the progression of the disease. As I understand it, the cellular degradation in Parkinson's disease is 80% complete prior to symptoms becoming evident. What sorts of research is the NIH supporting that would allow patients who are not symptomatic to be diagnosed in the early stages of this degenerative disease, such that there is a better chance for the neuroprotective agents to prevent the devastating symptoms?

Dr. Penn: NINDS is engaged in several areas of research designed to facilitate the diagnosis of individuals with Parkinson's disease (PD) before they show overt signs. NINDS is encouraging investigators to explore techniques such as functional magnetic resonance imaging (fMRI), which allows the activation of brain areas involved in motor control to be monitored, and the use of single photon emission computed tomography (SPECT) to assess changes in the subcellular components of dopamine nerve signaling. NINDS also supports many projects designed to characterize the biological basis of PD, including the contributions of genetics and external risk factors to the development of the disorder. Studies of parkinsonism involving affected individuals and their family members may also uncover leads for early clinical markers of the disease. Together, this knowledge will greatly enhance the ability of clinicians to assess the risk of PD - both in individuals who are predisposed to the disorder and in the general population - and to make more rapid and accurate diagnoses. In addition to these approaches, NINDS-funded researchers are exploring methods such as computer-aided analysis of fine motor movements, such as handwriting, to help in both the diagnosis of PD and the assessment of the effect of treatment. NINDS is currently evaluating options for enhancement of this research area, as the need for better disease assessment tools was identified as an area of high priority at the January 2002 Parkinson's Disease Agenda Implementation Review meeting.

MINORITY CANCER CENTERS

Mr. Cunningham: As you are aware, medically underserved communities and minorities are disproportionately affected by cancer. To begin to effectively address this problem, it seems important to develop expertise from within the community. Recently, I read that you had spoken to your advisory board of your plans to ramp up National Cancer Institute cancer centers program and focus on minority and underserved communities. Currently, are there any cancer centers at minority serving institutions?

Dr. von Eschenbach: Currently, there are no cancer centers at Minority Serving Institutions (MSIs), although Howard University has a Planning Grant (P20) to develop an NCI Cancer Center. The NCI believes that its new program to promote the development of partnerships between MSIs and NCI-designated Cancer Centers will have a significant impact on increasing the depth and breadth of cancer research at MSIs, increasing the number of minority investigators in cancer research and increasing the research at NCI Cancer Centers focused on minority health disparities. By the end of Fiscal Year 2002, five comprehensive partnerships will be funded: Johns Hopkins/Howard University; University of North Carolina/North Carolina Central University; Vanderbilt University/Meharray Medical College; M.D. Anderson/University of Puerto Rico; and University of Arizona/Northern Arizona State University. In addition to the comprehensive partnerships above, there are numerous planning grants being funded to develop comprehensive partnerships and to develop collaborative research projects and training programs. This program reaches out to more than 400 MSIs in the country and has been extremely well-received by both MSIs and NCI-designated Cancer Centers.

The Division of Cancer Prevention's Community Clinical Oncology Program (CCOP) provides support for expanding clinical research efforts in the community setting. Of the sixty CCOPs located in the U. S. and Puerto Rico, ten are Minority-based CCOPs. The Minority-based Community Clinical Oncology Programs (MBCCOPs) bring the advantages of state-of-the-art cancer treatment and prevention and control research to minority individuals in their own communities; increase the involvement of primary health care providers and other specialists with the MBCCOP investigators, providing an opportunity for education and exchange of information; and provide an operational base for extending cancer control and reducing cancer incidence, morbidity, and mortality in minority populations by accelerating the transfer of newly developed technology to widespread community application. Applicants for the MBCCOP must document that at least 40 percent of their newly diagnosed cancer patients are from minority populations. There are more than 110 minority investigators among the MBCCOPs which are listed below:

District of Columbia United (Howard University and Providence Hospital), Washington, DC
Gulf Coast, Mobile, AL
Louisiana State University Health Sciences Center, New Orleans, LA

Our Lady of Mercy Cancer Center, Bronx, New York
San Antonio, San Antonio,Texas
San Juan City Hospital, San Juan PR
University of Hawaii, Honolulu, HI (NCI-designated clinical cancer center)
University of Illinois at Chicago, Chicago, IL
University of New Mexico, Albuerque, NM
Virginia Commonwealth University, Richmond, VA (NCI-designated clinical cancer center)

PROSTATE CANCER

Mr. Cunningham: As a prostate cancer survivor, I am interested in new technologies being developed to prevent, detect, and treat prostate cancer. Can you please update me?

Dr. von Eschenbach: As you know, I am also a prostate cancer survivor. Prostate cancer is the single most common form of cancer in men except for skin cancers. As the U.S. population ages, the impact of prostate cancer will increase. No other cancer rises in both incidence and mortality with increasing age as rapidly as prostate cancer. Although significant progress has been made over the past several years to improve our understanding of prostate cancer, there is still much to learn with regard to its causation, early detection, improved diagnosis, treatment and prevention. The NCI is conducting a wide range of research addressing these issues.

IDENTIFYING AND DEVELOPING PREVENTION AGENTS

NCI is fostering investigator-initiated research to identify and characterize molecular targets for nutrients and further, to connect those targets with phenotypic outcomes in prostate cancer prevention. Both in vivo and in vitro studies to define molecular targets in terms of genetic and epigenetic events that are influenced by specific essential and nonessential nutrients will be undertaken. Candidate targets will not only be influenced by a nutrient but will also be closely linked to a significant proportion of prostate tumors and be relatively specific for prostate cancer across various genetic backgrounds.

NCI is conducting a number of early phase clinical trials of prevention agents. These include:

- Phase II randomized placebo-controlled trial of androgen deprivation therapy with flutamide for chemoprevention of prostate cancer in men with high-grade prostatic intraepithelial neoplasia (HGPIN). The trial was closed to accrual in September 2000 and follow-up is ongoing.
- Phase II prospective, non-randomized, controlled trial of sulindac sulfone (Exisulind), a novel proapoptotic (inducer of cell death) agent, prior to prostatectomy.

- Phase II randomized placebo controlled trial of the selective Cox-II inhibitor celecoxib prior to prostatectomy.
- Phase II placebo controlled trial of selenized yeast in men managed by watchful waiting with early prostate cancer.

NCI is also funding a number of large scale clinical trials looking at prevention agents. The Prostate Cancer Prevention Trial (PCPT) will determine if seven years of treatment with finasteride, a drug approved in 1992 to treat patients with symptomatic noncancerous enlargement of the prostate, prevents development of prostate cancer. Because finasteride reduces levels of the male hormone, DHT, it may prevent cellular changes leading to prostate cancer. Researchers are examining the point prevalence of prostate cancer after 7 years of intervention. The trial began recruitment in 1993 and the 18,862 men randomized to the trial are currently undergoing their end-of-study biopsies. About two thirds of the participants have completed their 7 years of drug and are now having their biopsies. Annual PSA and serum collection, tissue collection, and central review of the pathology will provide specimen resources and major databases to answer important questions beyond the primary endpoint. Results are expected in 2004.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) will determine if seven or more years of daily supplements of selenium and/or vitamin E reduces the number of new prostate cancers diagnosed in healthy men. The trial aims to substantiate earlier, separate findings suggesting that these naturally occurring nutrients and antioxidants may prevent prostate cancer. The trial is being conducted through NCI's Community Clinical Oncology Program network as an intergroup study coordinated by the Southwest Oncology Group at more than 400 sites in the U.S., Puerto Rico, and Canada. Enrollment started in August 2001 and more than 6,000 men age 55 and older had joined the trial as of Jan. 1 2002, with 9% being minorities. The enrollment goal is 32,400 men, with 20% minority representation, within 5 years. The largest prostate cancer prevention trial to date, SELECT also is designed to: assess the impact of selenium and vitamin E on the incidence of lung and colon cancer and survival; study molecular genetics of cancer risk and associations between diet and cancer; and examine quality of life. Data are expected beginning in 2012.

DETECTION TECHNOLOGIES

NCI is funding a variety of investigators who are developing and improving detection methods and technologies. These include computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), nuclear medicine techniques and ultrasound. Combining information from 2 different imaging modalities is also a promising approach. For example, we are funding a project investigating the value of imaging prostate cancer in a combined PET/CT scanner. The combination of MRI and MRS has shown exciting results in feasibility trials. Therefore, the NCI-funded American College of Radiology Imaging Network (ACRIN) is

beginning a large multi-center trial of combined MRI and MRS in prostate cancer. The imaging results from the combined MRI and MRS help guide biopsy in the prostate, assess extent of tumor (staging), and monitor for recurrence.

Imaging with molecularly targeted agents is another promising area. PET scanning with fluorodeoxyglucose (FDG) has not proven to be as effective for imaging prostate cancer as for other cancers. However, initial results with two other PET agents, fluorocholine and acetate, have been very promising. NCI is working with the developers of the fluorocholine compound to do the necessary testing for an IND and subsequent clinical trials, and we are working with several centers to begin a multi-center trial of carbon-11-labeled acetate for prostate PET scanning. In addition, NCI is funding investigator-initiated research projects using radiolabeled androgen receptor ligands. New MRI contrast agents that localize selectively in lymph nodes show promise for imaging metastatic prostate cancer in lymph nodes. This could help surgeons decide which nodes to remove or leave in.

NCI is also funding investigators who are working on other novel methods of detection such as elastographic imaging of prostate cancer, which measures the elasticity of tissue and presents the information on an imaging display. Optical technologies also appear promising for prostate cancer, but are in a very early stage of development.

PROSTATE CANCER SCREENING

The NCI is also funding the Early Detection Research Network, a national scientific consortium established to develop, evaluate, and validate biomarkers for earlier cancer detection and risk assessment. Within this network, the following projects are aimed specifically at prostate cancer.

-Genomics-based Assays for Detecting Cancer Proteins
-Early Detection of Cancer by Affinity Mass Spectrometry
-Identification of Prostate and Ovarian Cancer Markers
-Clinical and Epidemiological Center on Prostate Cancer
-San Antonio Center of Biomarkers of Risk for Prostate Cancer

The Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO) is a phase III randomized controlled trial that is evaluating the mortality and morbidity impacts of a group of screening tests for four common cancers that together account for nearly half of all cancer diagnoses and deaths in the U.S. Accrual of 155,000 participants was completed in June 2001, but data collection and analysis continue. Half of the participants, women and men ages 55 to 75, are randomized to receive screening tests (PSA and digital rectal exam, chest x-ray, flexible sigmoidoscopy, CA125 blood test, and transvaginal ultrasound); the other half receive the usual care given by their physicians. Both groups will provide information about their health every year for up to

16 years. This trial includes both a respository of tissues from participants and a large number of additional epidemiological studies. Preliminary data from the screening portion may be released in upcoming years, but the projected completion of the trial is in 2015.

TREATMENT TECHNOLOGIES

For the treatment of localized prostate cancer there have been continual improvements in the surgical techniques of nerve sparing radical prostatectomy. This operation can now be performed more safely with less morbidity, i.e, with less risk of incontinence and a greater likelihood of preserving potency.

Also under development are new techniques to perform radical prostatectomy with laparoscopic techniques. Although it is early in the development of this technology, a number of surgeons in the U.S. and abroad are very optimistic that the "minimally invasive" laparoscopic prostatectomy will provide a safe and effective method for prostatectomy that will have fewer side effects than current methods.

In addition 18 dose finding trials with 15 new agents of interest for future development in patients with prostate cancer were activated in 2001 by NCI. Of the agents previously in dose finding trials in 2000, 6 entered into specific phase II trials in patients with prostate cancer under NCI sponsorship, and 9 are entering industry-sponsored trials for patients with prostate cancer.

NCI is collaborating with the National Institute of Aging to fund grants in response to a request for applications for research on image-guided procedures for prostate biopsy or treatment. Thus far, 15 grants have been funded in the areas of image-guided radiation therapy, image-guided thermal ablation, image-guided biopsy and molecular imaging.

NCI is funding four additional research projects related to image-guided therapy that were submitted under a program announcement for novel imaging technologies, and four small business grants that are developing products related to imaging for diagnosis or brachytherapy of prostate cancer.

SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE (SPOREs) AND TRANSLATIONAL RESEARCH

The Specialized Programs of Research Excellence (SPOREs) were created in 1992 and focus on specific cancers. They serve as highly effective hubs for translational research, moving discoveries back and forth among laboratory, clinic, and population research settings. In the last two years, the number of prostate cancer SPOREs has expanded from 3 in 2000 to what the NCI hopes will be 11 by the end of 2002. Together, the eleven NCI SPOREs will conduct research on a broad array of new approaches designed to have the most immediate impact on improving cancer

prevention, early detection, diagnosis, prognosis and treatment. This expansion of the program will effectively triple these important translational research efforts; SPOREs are changing the way basic, clinical and population scientists work together as teams to tackle the big questions that will have the most immediate impact on reducing cancer incidence and mortality. The early phase of the prostate cancer SPORE program has already identified genes that place individuals at higher risk, new biomarkers that will improve diagnosis and prognosis (some of these appear to be more prevalent indicators in African Americans), initiated new therapeutic trials utilizing our knowledge of prostate cancer biology, and developed new cDNA and tissue microarray technologies that will lead to the discovery of many new potential biomarkers for prevention, early detection and diagnosis. Tremendous momentum has been initiated and with the addition of eight new SPOREs, the collaborative activities between SPOREs will increase and the process of discovery and applications will be magnified. The NCI prostate cancer SPOREs have also been linked collaboratively to the George M. O'Brien Urology Research Centers supported by the National Institute of Diabetes and Digestive and Kidney Diseases, providing critical scientific interactions between scientists dealing with hyperplastic phenonmen in the prostate gland, which may be the precursors to cancer, and those dealing directly with prostate cancer. The NCI believes that the infrastructure for making progress in the translational research of prostate cancer is in place and primed to have an impact on this dreaded disease in men.

DIABETES RESEARCH BUDGET

Mr. Cunningham: I understand that the budget for diabetes research at NIH is still well short of the recommendations outlined by the Diabetes Research Working Group in 1999. Where exactly does the budget for diabetes research stand today?

Dr. Spiegel: Diabetes research is supported by multiple NIH institutes and centers, as well as by diabetes voluntary groups and industry. NIH-wide funding for diabetes research is steadily increasing. In FY 2000, NIH spent $540 million to support diabetes research, and this amount went up to $688 million in FY 2001. Diabetes research support across the NIH will increase to an estimated $781 million in FY 2002, and an estimated $845 million in FY 2003. These increases have enabled the NIH to undertake many new and scientifically promising initiatives. However, the DRWG recommended nearly a fourfold increase in NIH funding for diabetes research from FY 2000 through FY 2004, and although all of the DRWG's scientific recommendations have merit, we have not been able to attain this type of fiscal growth within the context of our available budgetary resources and our responsibilities to fund other disease-oriented research programs within the NIH mission.

Mr. Cunningham: What scientific opportunities - in light of DRWG proposals - have gone unexplored or underexplored because of this budget shortfall?

Dr. Spiegel: Since the 1999 publication of the Diabetes Research Working Group's Strategic Plan, the NIH has launched many exciting new diabetes research initiatives. Using the funding increases provided by the Congress, we have also been able to sustain and expand ongoing efforts. I would not say that there is any area that has gone unexplored, but the rate of exploration has reflected the funds available. While we have addressed, to varying degrees, the many avenues of research identified by the DRWG, the scope and pace of our responsiveness have been a function of our budgetary resources, as well as our responsibility to support research in other disease-oriented programs within the NIH mission.

Scientific areas that can be productively pursued include the following examples. We would expand the number of clinical trials under way, particularly trials to compare various approaches to prevention and treatment of diabetes and its complications. Now that we have "proof of principle" from the Diabetes Prevention Program that type 2 diabetes can be prevented or delayed, we would accelerate efforts to develop cost-effective approaches to enhance adoption of lifestyle changes that can be used in work or community-based settings. We would enhance translational research to develop approaches to implement more broadly into practice the treatments that have proven useful in controlled clinical trials. We would increase the development of repositories and other resources to store and make available to scientists blood and tissue samples from clinical trials and other large clinical studies; while costly, the value of such shared resources cannot be overstated. We would greatly expand the collection and analysis of data in the consortia we are funding in the search for the causative genes in type 1 and type 2 diabetes and its complications. We would expand efforts to identify novel pathways and signals throughout the body that are affected by diabetes in order to develop new therapies.

RESEARCH HIGHLIGHTS SINCE DRWG REPORT

Mr. Cunningham: We are aware that you are now in the process of writing a follow-up document to the DRWG report, and that it will be available in August. We eagerly anticipate this material. In the meantime, can you give us some highlights of the research you have been able to pursue since the initial report's publication?

Dr. Spiegel: I am pleased to report that we have undertaken many important and promising new initiatives in response to the scientific recommendations in the DRWG's Strategic Plan. We have given priority to the five "Extraordinary Opportunities" singled out by the DRWG. These areas are: the genetics of diabetes; autoimmunity and the beta cell; cell signaling and cell regulation; obesity; and clinical research and clinical trials of critical importance. We have also addressed the areas identified by the DRWG as "special needs," including research on microvascular and macrovascular complications of diabetes, and diabetes in special populations-- including women, children, the elderly and minority populations. Many of our new initiatives with respect to the harnessing of

technology, the uses of research consortia, and support for a cadre of stellar investigative talent specifically address the DRWG's recommendations with respect to "resource and infrastructural needs."

While many of the new initiatives undertaken since the DRWG report was issued in 1999 will bear fruit in the future, in the few years since the DRWG report we have already seen important new information about diabetes emerge. One example is the dramatic finding in the Diabetes Prevention Program that relatively small changes in lifestyle–such as walking for 30 minutes five days a week and losing 10-15 pounds-- cut the rate of development of type 2 diabetes in high risk, overweight individuals by more than half. Another example is the demonstration, first in Canada and now confirmed in the NIDDK intramural research program, that islet transplantation can be successful in freeing patients with type 1 diabetes from the requirement for insulin injections or can dramatically reduce the need for insulin and improve control of diabetes. Continued follow-up of patients in the landmark Diabetes Control and Complications Trial (DCCT), which showed that improved blood sugar control could reduce eye, kidney and nerve complications by as much as 70 percent, has shown that these benefits persist and even increase long after completion of the trial. From basic research, we are now seeing significant progress in our understanding of the molecular basis of insulin resistance, a critical first step in the pathway that leads to type 2 diabetes. We have identified key signaling molecules which fat cells use to "talk" to cells in the liver and muscle that store, release and metabolize sugar and to communicate with areas in the brain that regulate appetite. Each of these signals provides a new potential target for development of new therapies.

Recent appropriation increases, coupled with special congressional funds specifically for type 1 diabetes research, have enabled a significant enhancement of NIH-wide diabetes research and we are making every effort to build upon our accomplishments and invest these resources wisely. Thus, we are now expanding our translational research effort to develop and test cost-effective strategies for implementation of the lifestyle changes that were shown effective in preventing type 2 diabetes in the Diabetes Prevention Program. Together with the National Center for Research Resources, we have established islet isolation centers to provide human pancreatic islets for future clinical trials to develop and test improved methods of islet transplantation. We are expanding research to develop approaches to preventing hypoglycemia or low blood sugar, because it is this problem that limits our ability to achieve the control of blood glucose that was proven to reduce complications in the DCCT. Together with the National Heart, Lung, and Blood Institute, we have initiated several major clinical trials addressing the cardiovascular complications of diabetes, which the DRWG underscored as the major killer of diabetes patients.

Mr. Cunningham: Additionally, can you highlight specific opportunities that you have not been able to pursue due to a lack of resources?

Dr. Spiegel: We have used the DRWG's Strategic Plan as a "scientific compass" to help us chart our program development efforts, to catalyze trans-NIH diabetes research initiatives, and to forge fruitful research collaborations with the diabetes voluntary community and with industry. While there is always room to do more, we believe we have been scientifically responsive to the broad goals of the DRWG, and to the scientific directions and priorities underscored by the DRWG's five-year Strategic Plan and we will continue to be so within the resources that are available to us. We are pursuing recommendations in all five areas of extraordinary opportunity, as well as responding to the recommendations for research on special populations. For example, in response to the burgeoning public health problem of type 2 diabetes in children, we are planning a clinical trial to compare methods of treatment for this disorder. We have also created clinical trials networks to address prevention of both type 1 and type 2 diabetes in children. Within the resources available to us, we will prioritize among the trials proposed to be conducted in these networks. Burgeoning areas of basic research involve use of "knock out" mice to dissect the roles of multiple signaling molecules that are involved in control of blood sugar and regulation of appetite and metabolism, and the use of new proteomic and genomic technologies to study patterns of gene expression in tissues affected in diabetes. Studies with these cutting-edge technologies are costly, and we are pursuing them to the fullest extent possible with available resources.

DISTRIBUTION OF ADDITIONAL RESOURCES

Mr. Cunningham: It is clear that the current budget for diabetes research at both NIH as a whole and at NIDDK is well below the budget proposed by the DRWG report. If you had additional resources to conduct more diabetes research, would you be able to effectively use and distribute these funds?

Dr. Spiegel: We have used our existing funding to initiate and expand research consortia, providing networks of investigators who are well-positioned to effectively employ new resources as they become available. We now have such networks in place in each of the five critical areas identified by the DRWG. For example, we have created a new international type 1 diabetes genetic consortium and a consortium to study genetics of diabetic nephropathy and other complications, as well as increasing support of the type 2 diabetes genetic linkage consortium. Another consortium is identifying and characterizing the genes involved in pancreatic endocrine development and function. Each of these consortia is working to increase the rate and scope of collection and analysis of genetic data to the fullest extent possible with existing resources. Similarly, we have created networks and consortia to pursue a range of clinical investigations and clinical trials. Other consortia focus on developing and characterizing animal models of diabetes. Our research centers provide shared resources for groups of collaborating investigators. Each of these groups and consortia has identified research opportunities and set priorities in pursuing them. The existence of these consortia and their ongoing consideration of newly emerging opportunities provide for flexibility in most effectively utilizing resources as they become available. In addition we have deployed new resources to attract new investigators to diabetes

research–both talented newly trained scientists and established scientists with expertise in technologies applicable to diabetes. As additional resources become available, we are able to mobilize these scientists through targeted solicitations focused on areas of opportunity identified by the DRWG.

In addition, new opportunities have emerged since the DRWG strategic planning effort. We are now in the process of preparing a progress report requested by this Subcommittee on the program efforts, scientific advances and new opportunities in diabetes research since issuance of the DRWG's Strategic Plan in 1999. In doing so, we are consulting broadly with experts in the field–through conferences and workshops, as well as ad hoc planning meetings–and we are receiving many recommendations for future initiatives that could be productively pursued.

Mr. Cunningham: What specific research opportunities would you pursue with additional resources?

Dr. Spiegel: With additional resources, we would expand the scope and pace of initiatives we have begun in response to the DRWG's 1999 Strategic Plan, and frame initiatives to take advantage of new opportunities that have emerged since then–as identified by external scientific experts in the diabetes community. In preparing the mandated progress report for this Subcommittee, we have received numerous recommendations for initiatives that would expand the pace and scope of our efforts to elucidate the genetic basis of diabetes, understand how diabetes affects the many tissues it alters and damages, identify new methods to prevent the increasing epidemic of obesity that is fueling the increase in diabetes, and test promising new approaches to prevent diabetes and its complications. Thus, additional funding should extend the fundamental knowledge base and develop more effective treatment and preventative approaches.

ISLET TRANSPLANTS FOR TYPE 1 DIABETES

Mr. Cunningham: It is my understanding that less than 2000 pancreases are available every year for clinical trials involving the transplantation of insulin producing cells into individuals with juvenile diabetes. What is the most promising research to solve this supply problem if and when will these transplants are ready to be applied to the general population of individuals suffering from juvenile diabetes? Will stem cell research play a role?

Dr. Spiegel: In type 1 diabetes, the immune system's destruction of insulin-producing beta cells in the pancreas leads to lifelong dependence on insulin injections for survival. While external insulin administration is life-saving, it is far from an optimal way to address this disease. To find more effective therapeutic and prevention strategies, researchers are seeking to restore natural insulin-producing ability to type 1 diabetes patients through the transplantation of insulin-producing cells, found in clusters called islets, within donor pancreatic tissue. Based on preliminary results, this approach

appears highly promising. At this point in time, we believe that early clinical results provide an important "proof of principle" that islet transplantation can be a viable treatment for type 1 diabetes. This research avenue thus offers tremendous hope to the estimated one million Americans with type 1 diabetes.

Unfortunately, the number of pancreases donated annually would not be sufficient to provide islet transplantation therapy to all patients with type 1 diabetes for whom this therapy could be a future medical option. To address this supply shortage, the NIDDK has therefore launched a multifaceted initiative to learn everything possible about insulin-producing cells through the "Comprehensive Beta Cell Project." This project will further understanding of beta cell biology, and help define the patterns of gene expression at every stage in the development of these insulin-producing cells within the pancreas. With the knowledge generated from these studies, researchers hope to develop ways to generate an unlimited supply of new beta cells for transplantation therapy in type 1 diabetes.

In parallel with these efforts, we are also pursuing stem cell biology as a potential source of islets for cell-based therapy of type 1 diabetes. Our initiatives in this area are consonant with extensive previous work on bone marrow-derived and other adult stem cells, such as those isolated from pancreatic ducts, and with the President's decision to permit NIH funding of research using certain existing human embryonic stem cell lines. These studies of stem cells may illuminate ways in which we can "coax" these undifferentiated progenitor cells to become insulin-producing beta cells that could be used in transplantation therapy of type 1 diabetes.

VACCINE RESEARCH PROGRAM

Ms. Pelosi: It is my understanding that the Administration has decided to move the well regarded military HIV vaccine research program to the NIH. Could you tell us about why this transfer is being made? Will the funding and staffing of the DOD vaccine program be maintained at NIH? Will you move forward with the Phase 3 clinical trial that DoD has planned for Thailand?

Dr. Fauci: The White House Office of Management and Budget directed the transfer of oversight and management for the DoD HIV Research and Development Program of the U.S. Army Medical Research and Material Command (USAMRMC) to the NIH in January 2002. NIAID, which has the primary responsibility for HIV/AIDS research within the NIH, will assume responsibility for this program beginning October 1, 2002.

NIAID and USAMRMC have a common goal: to prevent the further spread of HIV/AIDS by developing safe and effective vaccines, other prevention strategies and innovative HIV treatments. The research activities of both groups are complementary and will be effectively integrated. The major difference between the two is the constituencies they serve: the USAMRMC research program primarily serves young, healthy adults on active military duty who are subject to worldwide development, while the NIAID research program serves all civilian age groups and addresses all HIV-associated conditions, such as opportunistic infections and other AIDS complications. NIAID will continue to support HIV research and development that is deemed relevant and supportive of the military mission.

USAMRMC's experience conducting international drug and vaccine development and testing and its established collaborative ties in many parts of the world will enhance NIAID's expanding international efforts. In turn, USAMRMC programs will benefit from NIAID's vast HIV/AIDS pre-clinical research program, which is integrated into NIAID's comprehensive HIV/AIDS effort.

Since 1993, NIAID and USAMRMC have collaborated significantly on complementary research programs. The two Institutes are collaborating on a large international clinical trial of IL-2 in people infected with HIV. By formally integrating the experience, expertise, research infrastructure and resources of both Institutes, the merger will ensure that the U.S. government HIV research effort is comprehensive, efficient and coordinated.

During Fiscal Year 2003, NIAID will continue to fund and support operations of the current USAMRMC HIV Vaccine research program, including the Phase III HIV vaccine efficacy trial in Thailand that is scheduled to commence later in 2002. We will continue to move forward with clinical trials in Thailand.

HIV/AIDS RESEARCH

Ms. Pelosi: NIH has been urged in report language to consider ways in which the five year plan for the CFAR (Center for AIDS Research) program can be modified to balance the need to expand the number of Centers with the need to adequately support the leading AIDS research institutions with the core center mechanisms that they need to efficiently pursue AIDS research. What has the NIH done to ensure that leading AIDS research institutions have adequate core resources to conduct their research?

Dr. Fauci: The Centers for AIDS Research Program (CFAR) has expanded over the last few years to include 19 funded sites around the country (see http://www.niaid.nih.gov/research/cfar/home.htm), which encompass a large majority of HIV/AIDS funded investigators. To ensure adequate funding to these leading AIDS research institutions, we are considering several options for revising the new CFAR solicitation in the FY 2003 Program Announcement, including mechanisms for flexibility in the current $1.5M cap.

MICROBICIDE RESEARCH

Ms. Pelosi: We know that NIH leadership remains key to addressing the research hurdles in HIV prevention. Increasingly, the epicenter of the HIV epidemic in the developing world is among women--- and from what the research tells us, there is no question that female-controlled HIV prevention methods such as microbicides are vital to controlling the spread of HIV.

Microbicides research at NIH is conducted under several institutes, with no single line of administrative accountability and no specific funding coordination. In addition, other federal agencies such as CDC and USAID undertake significant microbicides activity, with no overall federal coordination or planning. The Subcommittee has asked HHS and NIH to lead the effort to coordinate federal research efforts in this field to address the inefficiencies and duplication of effort.

What progress has been made in establishing a coordinated research and development program at NIH?

Dr. Fauci: The investment in microbicide research, including basic, preclinical, clinical, and behavioral sciences, is an integral and essential component of the overall Federal HIV prevention science agenda. The Office of AIDS Research (OAR), located in the Office of the Director of the NIH, directs the planning, coordination and integration of all AIDS research activities, including microbicide research, across the NIH Institutes and Centers. The OAR is committed to coordinating this priority area of research across the NIH Institutes and Centers and other federal agencies involved in the development of these products.

Microbicide research requires a complex multidisciplinary and multisectoral approach by teams of scientists with expertise ranging from the biomedical to the behavioral and social sciences, to experts in clinical trials and drug discovery and development. Because of uncertainty about the potential market, microbicide research has attracted involvement of only a minimal number of small pharmaceutical and biotechnology companies with limited funding. Thus, the OAR is also working to increase interest among scientists in conducting research in this extremely challenging area.

Ms. Pelosi: What progress has been made in microbicides research and development?

Dr. Fauci: To date, NIAID researchers have examined over 1825 unique compounds to determine their ability to block HIV transmission from infected T cells to cultures of cells representing those that line the human cervix. In 2001, NIAID funded researchers developed a new assay to monitor the activity of potential microbicides in the conditions that mimic the vaginal environment.

NIAID evaluated 11 candidate microbicides for safety (effects on surface tissues and microenvironment of the cervix and vagina.) in pig-tailed macaques through a contract with the University of Washington. Three of these candidates have also been tested for efficacy against chlamydial challenge in the same pig-tailed macaque model, and several are entering clinical trials in the HIV Prevention Trials Network (HPTN), a global clinical trials network designed to evaluate non-vaccine HIV prevention strategies, including topical microbicides.

A number of promising topical microbicide candidates are in various stages of testing.

- BufferGel (an acid-buffering gel that helps maintain the normal acidic environment of the vagina during coitus in order to disrupt the transmission of acid-sensitive STD pathogens, such as HIV) has been tested for safety in clinical trials through NIAID's HIV Network for Prevention Trials or HIVNET. The results indicate that it is nontoxic and well tolerated; it will continue to be evaluated for safety and effectiveness.

- Different strengths of PRO 2000/5 Gel (P) (a synthetic compound that works by inhibiting HIV attachment and fusion) were recently tested; the product was well tolerated with no serious side effects. Since PRO 2000 was safe and well tolerated (under the specific conditions of this study), NIAID will continue to evaluate it for its widespread effectiveness and potential use.

- PMPA Gel [9-(2-phosphonylmethoxypropyl)-adenine] (which inhibits HIV replication) is currently being tested in a phase I study. PMPA gel has prevented the infection of female monkeys with simian immunodeficiency virus (SIV), a relative of HIV, when they were exposed to SIV in the vagina.

MAMMOGRAPHY

Mrs. Lowey: Dr. von Eschenbach, I would first like to welcome you to your new position. I look forward to working with you on such an important issue, and I know my colleagues and I share your excitement in this field. My question to you is about mammography. I was glad to see you join with Secretary Thompson in reaffirming the recommendation that women should still undergo an annual mammogram after age 40. It is important that women have all the facts about the procedure, but also that they understand that it is the best tool we have right now to detect breast cancer early.

However, I think that the current debate over the data on mammography misses the point. I think it's time for the next generation of early detection. I know that researchers across the country are looking at promising new methods. Despite these advances, even the new technologies have glaring shortcomings. Experts and scientists agree that we still have not found the 21 st century early detection method we need.

I believe that we must substantially increase and accelerate research into these and other breast cancer screening techniques. What do you think the next steps will be? What methods show the greatest promise now and in the future? What leadership will NIH provide in this area?

Dr. von Eschenbach: The NCI is taking a very active role in both improving on currently available technology as well as developing new methods for the early detection of breast cancer.

Digital mammography is similar in many ways to conventional (film-screen) mammography except that the image is captured on an electronic receptor (also called a detector) instead of on film. The electronic receptors capture more information than film. The electronic image can be processed in a variety of ways by computer software, and pilot data suggest that this computerized image processing will result in detection of more cancers and elimination of more false positives than in conventional mammography. Furthermore, software can be used to automatically detect suspicious areas on the mammogram and call these to the attention of the radiologist. This should result in more consistent interpretation of mammograms and fewer missed cancers.

Different manufacturers use different technologies for their electronic detectors, and it is not yet clear whether they are all equal to each other and better than conventional mammography. Two technologies have been approved by the FDA, and two others are available in test units at several sites in the United States. NCI is funding a large trial comparing digital mammography with conventional mammography. Technologies from four different manufacturers are included. The trial will accrue approximately 49,000 women at 19 sites in the United States over 2 years. Results should be available in approximately 3 years.

There are several imaging technologies that are being studied or proposed as alternatives or adjuncts to mammography for early detection of breast cancer. Two imaging technologies that are relatively mature and have been suggested for early breast cancer detection are ultrasound and MRI. NCI is funding a cooperative group of fourteen institutions doing a pilot study of MRI for early breast cancer screening in women at high risk. That pilot study is almost complete and results are expected within a year or two. Pilot studies of ultrasound for breast cancer detection have been completed and show some promising results, although somewhat dependent on the experience of the people doing the ultrasound. NCI funds a cooperative group for multicenter imaging clinical trials called the American College of Radiology Imaging Network (ACRIN). Within ACRIN there is now a protocol development team putting together a proposal for a large multicenter trial of ultrasound for early breast cancer detection.

Computed tomography (CT) provides 3-dimensional images of body structure. Recent advances in CT technology make it possible to acquire CT images in seconds, and use much lower doses of radiation than previously. The potential advantage of using CT for breast imaging is that it could be done without applying compression to the breast. NCI is funding a Bioengineering Research Partnership (BRP) grant for development of a dedicated breast CT scanner that could produce 3-D images of the breast using no more radiation than is used in conventional mammography. Such a device could potentially be used for screening, and might find increased acceptance among women compared to mammography because of the absence of the need for compression.

There are several less mature imaging technologies that have been proposed or are being investigated for early breast cancer detection. Thermography is a technique that detects changes in skin temperature caused by changes in blood flow. Thermography was tested for early breast cancer detection in the 1970's but abandoned because of poor sensitivity. In recent years the FDA approved two new devices for thermography. However thermography is still not widely accepted for screening because of high false positive rates and low sensitivity. NCI is funding some investigator-initiated research projects that seek to improve thermography for breast cancer detection.

Electrical impedance devices work by passing a small electric current through the breast and measuring the voltage changes on the surface of the skin. An FDA approved device is commercially available, but is not widely used for screening because of relatively poor sensitivity and high false positive rates. For comparison, the sensitivity and specificity of ultrasound and MRI have both been better in pilot trials than the corresponding values for thermography or electrical impedance.

Nuclear medicine techniques are used to help to distinguish benign from malignant breast masses, but so far have not been shown to be practical for wide spread screening. Scintimammography using a radiolabeled compound called sestamibi is useful in evaluating masses detected by mammography or by physical examination, but

it is not considered useful for screening because it does not reliably detect cancer smaller than one centimeter. Similarly, PET scanning with a radiolabeled glucose compound is useful for evaluating breast abnormalities, but is not considered useful for screening because it does not reliably detect cancer smaller than one centimeter, and it is relatively expensive. NCI is funding some investigator-initiated research projects that aim to develop dedicated PET scanners for the breast that would make the examination considerably cheaper and would have improved resolution for finding small cancers. If these goals are achieved, then PET scanning might be a reliable screening modality.

There are a variety of optical technologies that use light from lasers in the visible spectrum or in the near-infrared spectrum. These can detect differences between oxygenated and non-oxygenated hemoglobin, or can detect signals from optical contrast agents that have been injected. These technologies are in an early stage of development and so it is difficult at this time to predict whether they will be feasible for screening. However some early results look very promising and optical technologies have the advantages of being relatively inexpensive and not using ionizing radiation. NCI funds several research projects looking at a variety of different optical technologies, and will soon issue a Request for Applications for a network for optical technologies development.

There are a variety of other imaging modalities which are in very early stages of development for possible detection of early breast cancer. These include technologies such as magnetic resonance spectroscopy, magnetomammography, Hall effect imaging (passing an electric pulse through tissue while exposed to a magnetic field), thermo-acoustic computed tomography, and focused microwaves for imaging. Again, NCI funds a wide variety of research projects on these imaging technologies, including a program project entitled, "Alternative Breast Cancer Imaging Modalities." It is too early to predict whether any of these will actually become useful for early breast cancer detection.

Many imaging modalities rely on the presence or absence of structural change for detecting abnormality. One of the uncertainties about a structural change is whether it represents a biologically aggressive or non-aggressive cancer. Better understanding of the biology of breast cancer is needed. As our knowledge about the biology of breast cancer improves, some of the novel imaging techniques described above that can detect functional changes may become more feasible and indicate lesions that definitely need to be removed. In the near term, it is likely that MRI and ultrasound will be found to be useful for screening certain populations of women for whom mammography is inadequate, such as young women at high risk and women with very dense breast parenchyma.

In addition to imaging technology, NCI is investing in new biologic tests to improve our ability to identify cancer cells in their earliest possible stages of development. Among the research being supported:

Molecular Analysis - NCI's Innovative Molecular Analysis Technologies Program (IMAT) supports the development of non-invasive techniques for identifying molecular changes that distinguish cancer cells from normal cells. More than 100 research projects are under way, focusing on new approaches to analyze DNA, RNA, and proteins.

Proteomics: Finding Protein Patterns - Proteomics is the systematic study of protein expression and function. In the Clinical Proteomics Program, a joint initiative of NCI and FDA, researchers are discovering differences in patterns of protein in the blood from cancer patients compared to people without cancer and applying this knowledge to early detection of breast cancer.

Biomarkers - NCI's Early Detection Research Network (EDRN) is the first comprehensive network to develop and validate early detection markers for cancer. Researchers are studying a variety of molecules, proteins, genes, and other biological substances that may be the earliest warning signs that normal cells are on the road to becoming cancerous. Their discoveries are then translated into methods for detecting warning signals, sometimes even before full-blown cancer can develop.

Finding Fingerprints of Cancer Cells: The Molecular Classification of Tumors - All cells have unique "signatures" - special characteristics related to which genes are active and which proteins or other products the cell manufactures. During the transformation of a normal cell to a cancer cell, the cell's signature changes, and the change becomes a signal of the presence of cancer. Researchers are developing profiles of molecular alterations in human tumors, such as breast cancer, using DNA, RNA, or protein-based technologies. This technology holds promise for improving the early detection, diagnosis, and treatment of cancer.

Over the years, researchers have focused on examination of cells shed by breast tissue into the ducts. Investigators have now developed techniques for collecting nipple aspirates and ductal lavage and hope that it may be possible to evaluate suspicious breast masses detected by mammography by analyzing these secretions. It may be possible to spare at least some women the need to undergo a surgical biopsy.

NCI is playing a leadership role for the Interagency Council, a newly created multi-agency group designed to serve as a sounding board for investigators and manufacturers attempting to take emerging medical imaging technology to market. It consists of a core staff from the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS) and NCI with experience and knowledge concerning the decision-making processes for their agency for medical imaging products. Additional agency staff may be added to the core group on specific matters when needed. The purpose of the Council is to provide multi-agency advice that may help guide imaging technology developers in the fight against cancer. The Council will

provide advice on projects or project proposals brought voluntarily by investigators and technology/device developers in industry and academia. It offers a new, multi-agency perspective to the communication with government agencies that is already available to investigators and companies.

The three agencies participating in the Interagency Council all have different roles in the development of medical imaging technologies. NCI has created and is expanding a Biomedical Imaging Program. This effort currently funds innovative device and technology development, small animal imaging, in vivo cellular and molecular imaging centers, and a clinical trials imaging network (ACRIN). NCI will provide input on scientific and medical issues, information on the initiatives and research resources available to fund or develop imaging technologies, explain the process for gaining access to such resources, and facilitate future interactions of imaging technology developers with NCI staff or with other NCI-sponsored investigators.

The NCI has organized a unique Imaging Forum to bring technology developers from academia and industry together with funding agencies, regulators, and reimbursement sources. These partnerships promote communication and progress in the development, testing, and adoption of new imaging modalities and applications.

BIOMARKERS FOR CANCER

Mrs. Lowey: The advocacy community sees the identification of biomarkers for breast cancer as the gold standard for early detection. Finding a non-invasive but accurate blood test would be a tremendous achievement. I know that there is research ongoing to find biomarkers for all types of cancer. What is the state of that research? In particular, what work is ongoing in breast cancer? How far away are we from developing such a test?

Dr. von Eschenbach: The NCI is sponsoring a wide range of research to discover biomarkers for use in the early detection of all cancers, including breast cancer. Last month the NCI, along with the Food and Drug Administration (FDA) reported that patterns of proteins found in patients' blood serum may reflect the presence of disease. In the past we focused on funding a single protein, like CSA or PSA, but now we are using computer-based analysis of the patterns of certain proteins that reflect the presence of cancer. In the study, scientists were able to detect ovarian cancer even at early stages and this new diagnostic concept is potentially applicable to any type of disease.

Using a test that can be completed in 30 minutes using blood obtained from a finger stick, researchers were able to differentiate between serum samples taken from patients with ovarian cancer and those from unaffected individuals. The research, a joint effort between the FDA, NCI and Correlogic Systems Inc., unites two exciting disciplines: proteomics - the study of the proteins inside cells - and artificial intelligence computer programs.

The diagnostic test relied on software that was able to detect patterns of key proteins in the blood. Using a sophisticated artificial intelligence computer program developed by Correlogic, scientists were able to "train" the computer to distinguish between patterns of small proteins found in the blood of cancer patients vs. control samples. The artificial intelligence program identified a pattern consisting of only a handful of proteins, among thousands, that could be used to distinguish between women with ovarian cancer and women with non-cancerous conditions. The idea that rather than a single biomarker, an entire pattern of proteins contains important diagnostic information, is an exciting new paradigm.

An important finding was the ability to correctly identify, in a small sample of patients, all stage I ovarian cancer cases. Currently, more than 80 percent of ovarian cancer patients are diagnosed at a late clinical stage and have a 20 percent or less chance of survival at 5 years. In contrast, the 20 percent of women diagnosed with early-stage disease have an excellent prognosis, with over 95 percent alive at 5 years after diagnosis. The results of this study indicates that proteomic technology may help clinicians diagnose the disease much earlier than current methods.

Further study is needed to confirm the sensitivity and accuracy of this technique as a diagnostic tool. We hope that by combining the proteomic approach with other methods of ovarian cancer diagnosis, such as ultrasound, its accuracy can be further improved. We must validate the promise of these results in a large, multi-institutional trial. Such trials are under way at the NCI, evaluating proteomics both alone and in combination with current screening methods for ovarian cancer.

Mammography is a useful test, but not the answer to breast cancer. The new frontier in early detection research is the development and clinical testing of biomarkers. It is the goal of Early Detection Research Network (EDRN) to identify proteins in breast fluid or blood that can provide a "biological profile" for early detection of breast cancer. The long-term goal is to refine this profile to distinguish curable, clinically important breast cancers.

To develop this profile, investigators at the Johns Hopkins University are using SELDI (surface enhanced laser desorption and ionization spectroscopy). SELDI is a novel molecular assay that rapidly produces a profile indicating the relative amounts of different proteins in a sample, such as breast fluid. By comparing samples of breast fluid (or blood) from women with early, curable cancers to samples from women with normal breasts, we hope to identify specific protein patterns that consistently appear in one group but not the other. Data from this molecular biological assay technique are analyzed with powerful mathematical tools that have the ability to find consistent patterns out of tens of thousands of data points.

By utilizing large expression databases, investigators at Duke University have found two new genes (BU101 and BS106) that appear to be expressed primarily in breast cells (both benign and malignant). Since breast cells are not found in the blood of

healthy women, we postulate that the presence of these gene products will be a signal that there is a growth abnormality in the breast, most likely cancer or early precancerous changes. The scientists have developed a series of reagents and assays for these two new genes with the goal of detecting very low levels of these gene products in the blood. Two other markers have been developed independently (cytokeratin and mammaglobin) and have been used in a similar fashion for the detection of circulating breast cancer cells. Researchers are comparing the new markers to these established markers in order to determine their relative sensitivity and specificity. To date, results indicate that no one marker will achieve the desired goal of detecting every cancer; however combinations of these markers may be able to detect virtually all breast cancers.

The NCI Innovative Molecular Analysis Technologies (IMAT) program is focused on the development and pilot applications of novel technologies that will support the molecular analysis of cancers and their host environment in support of basic, clinical, and epidemiological research. Technologies solicited include those that are suitable for the detection of alterations and instabilities of genomic DNA; monitoring of the expression of genes and gene products; analysis and detection of the cellular localization, post-translational modification, and function of proteins; and monitoring of major signal transduction networks involved in cancer.

Within the IMAT program there are efforts directed toward the identification of biomarkers for breast cancer. Two of the efforts analyze nipple aspirate fluid, and the other three work at the protein and gene level.

Howard University and Georgetown University are collaborating on an effort to detect estrogen receptor (ER) isoform changes in ductal lavage and nipple aspirate fluids. This collaborative effort will focus on establishing the feasibility of profiling ER isoforms at their mRNA levels in ductal lavage/nipple aspiration samples by RT PCR methods. The hope is that by combining these two research efforts, the technology of evaluating nipple aspirate fluid for the detection of breast cancer will move closer to clinical application.

NCI-funded researchers are also working on detection at the protein and gene level, which may lead to detection much earlier in the progression of cancer. This research is more fundamental, and these efforts may take longer to achieve clinical application than the Georgetown/Howard study.

It is very difficult to predict how soon we can develop these tests. The EDRN studies are currently in the discovery phase, i.e. enrolling women with breast cancer and normal breasts, collecting samples of their breast fluid and blood, and analyzing the protein patterns in each woman. Preliminary data from a small number of women shows that there are consistent differences between cancerous and normal breasts in some proteins. We hope to complete the discovery phase of the research in 2 years. An additional year will be needed to complete analyses and validation of the data. At the end of this time we expect to be able to mount a validation study to test the protein

profile defined by the research. It's possible that 5 years from now we may have completed a clinical trial to test a protein profile, in breast fluid or blood, for early detection of breast cancer. All five of the above mentioned IMAT programs were initiated in the late fall of 2000, and are still in the proof of principle stages.

MICROBICIDES

Mrs. Lowey: Dr. Fauci, as you know, I am very interested in the issue of microbicides. I know that NIAID is working to develop a vaccine to combat HIV/AIDS. However, we also know that it is very difficult for women to protect themselves against the disease, particularly in the developing world.

First, how many staff at NIAID are working exclusively on microbicides, and how are you making changes to reflect the increased funding NIAID has directed for microbicides? Second, I understand that there are a number of microbicide candidates that appear safer and less irritating that earlier products. What funding will be necessary to bring these products into clinical testing?

Dr. Fauci: Intramurally, we currently devote four full-time equivalent positions to topical microbicide research with plans to hire additional staff including a medical officer and behavioral scientist who would be predominantly working on topical microbicide development. Microbicide research is multi-disciplinary in nature and in addition to those specifically devoted to topical microbicides, staff throughout the Division of AIDS continue to make substantial contributions to our research efforts in this area. For example, it is particularly important, to utilize staff with broad expertise in the process of drug discovery. This is because the screening of potentially useful topical microbicides can be pathogen-specific (based on the different properties of the sexually transmitted infectious agent) and requires knowledge about drug targets for both HIV and other sexually transmitted diseases. Similarly, staff with expertise in preclinical toxicology help ensure that critical testing occurs, and medical officers facilitate collaboration with investigators and industry in the design, management, and analysis of clinical trials.

In combination with our staff expansion, we are starting a major research initiative in FY 2003 that seeks to expand the number and scope of candidate microbicides in the "pipeline" to an advanced development stage and early human clinical trials; encourage a combination of approaches to prevent attachment of HIV at multiple points of entry; attract the private sector to microbicide development; and fill fundamental and epidemiological gaps critical to the through evaluation of microbicides in clinical trials.

It is difficult to estimate the amount of financial support that would be needed to bring current and future candidates through clinical trials. Our estimate is that to take one candidate topical microbicide from preclinical testing through all phases of clinical

evaluation (from early safety studies to efficacy and effectiveness trials) would be between $60 and $80 million over 10-15 years. Not all of this cost would necessarily be expected to be born by the Federal Government.

Because any individual candidate can be formulated in different ways that may affect acceptability as well as effectiveness, the full costs of development may well exceed this estimate. In addition, the most effective products may be ones that combine multiple active agents and, again, the cost for development would exceed that of a single agent because of the need to repeat for both single agents and the combination the many steps involved in preclinical and clinical testing.

Mrs. Lowey: Dr. Fauci, the AIDS Division's vaccine program seems to be working successfully. Specifically, I understand the program is focusing on a product development strategy and has devoted significant dedicated staff to it. Has NIAID considered a similar approach for microbicides?

Dr. Fauci: Yes. The Division of AIDS is in the process of replicating several programs for topical microbicide research that have been effective in advancing HIV vaccine research. For example, we recently established the Integrated Preclinical/Clinical Program for HIV Topical Microbicides, which is modeled after a similar program for vaccines. The program will support translational, iterative research, whereby results from pilot clinical trials will be used to optimize product development. Another highly successful model is that of the Innovation Grant Program, which has supported research on novel HIV vaccine concepts. We have created a similar program that encompasses topical microbicide development and anticipate making the first awards in early FY 2003.

FOOD ALLERGIES

Mrs. Lowey: Dr. Fauci, I remained concerned for the millions of Americans who suffer from food allergies. Last year, the subcommittee requested that NIAID convene a panel of experts to review current research in food allergies and recommend a research agenda for the future. What progress has been made on this?

Dr. Fauci: The NIAID will convene a panel of experts in FY 2003 to identify key gaps and opportunities in food allergy research. This panel will also review the capacity of genetically engineered foods to induce allergic responses in susceptible individuals. It is anticipated that new research initiatives will be developed based on the recommendations of this panel.

INFLAMMATORY BOWEL DISEASE

Mrs. Lowey: Dr. Fauci, there are almost one million in this country who suffer from Crohn's disease or ulcerative colitis, collectively known as inflammatory bowel disease. Would you please tell us what role the immune system plays in the

development and progression of these diseases and update us on NIAID's IBD research portfolio?

Dr. Fauci: Autoimmune diseases result from a disordered attack of the immune system on the body's own tissues. In inflammatory bowel disease, cells of the immune system attack the intestinal tissues. Increasing evidence indicates that IBD results from a combination of genetic susceptibilities coupled with environmental or infectious triggers that contribute to the development of the disordered immune response that begins in the gastrointestinal mucosa. Further definition of the role of each of these factors and the mechanism of the immune response in these diseases should allow development of improved therapies and preventive strategies. The role of the immune system in these diseases is highlighted by the recently demonstrated efficacy of an immune-modulating therapy [anti-TNF (tumor necrosis factor)] in Crohn's disease.

The NIAID supports a broad program of research in autoimmunity and autoimmune diseases, including basic research, and animal and human studies. In FY 1999, the NIAID established the Autoimmunity Centers of Excellence to support collaborative basic and clinical research on multiple autoimmune diseases, including single-site and multi-site pilot clinical trials of immunomodulatory therapies. Two of the four Centers have the capacity to conduct clinical trials in IBD. The NIAID, NIDCR, and the Crohn's and Colitis Foundation of America co-sponsored the research initiative, "Innovative Research in Human Mucosal Immunity," to promote exploratory and innovative investigations in this important area. Eighteen awards were made in FY 2000, six focused specifically on IBD.

In FY 2001, NIAID, with several other NIH Institutes and Offices and the Juvenile Diabetes Research Foundation, established the Cooperative Study Group for Autoimmune Disease Prevention to conduct basic research leading to the development of new targets and approaches to prevent autoimmune disease and to evaluate novel approaches in pilot and clinical studies.

Under an NIAID Request for Applications, entitled "Hyperaccelerated Award/Mechanisms in Immune Disease Trials," support is being provided for mechanistic studies associated with clinical trials of immunotherapies for immune-mediated diseases, including such autoimmune diseases as inflammatory bowel disease. Requirements for applications are abbreviated, submitted monthly, receive an expedited review, and are awarded within 13 weeks of submission.

In FY 1999, the NIAID participated in two trans-NIH solicitations for research on the role of environmental and infectious agents in the pathogenesis of autoimmune diseases. Research projects were funded to study the immune mechanisms by which normal bowel flora can stimulate a chronic inflammatory response in the gastrointestinal tract of genetically susceptible animal models. Studies are underway to extrapolate these findings to human disease. In FY 1999, the NIAID established the Multiple Autoimmune Diseases Genetics Consortium (MADGC) to collect clinical information,

and DNA and cell samples for genetic studies from families who have members with more than one autoimmune disease, including IBD. Clinical information and specimens will be available to investigators to support studies of the genetics and etiology of these diseases.

In FY 2001, the NIH Autoimmune Diseases Coordinating Committee (ADCC), chaired by the NIAID, began work on a strategic research plan for autoimmune diseases, including IBD, as required by the Children's Health Act of 2000 (P.L. 106-310). The ADCC will transmit the plan to Congress in Spring 2002.

The NIAID's future plans in autoimmunity and autoimmune diseases include: the renewal and expansion of the Autoimmunity Centers of Excellence, in FY 2003, to support basic research and new and ongoing clinical trials of immune therapies for multiple autoimmune diseases, including IBD; and funding applications received in response to the RFA "Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection." These grants will identify and validate the role of pathogens in chronic diseases including IBD.

The major challenges facing autoimmune diseases research today are: 1) development of a mechanism-based, conceptual understanding of autoimmune disease; 2) translation of this knowledge into new, broadly applicable strategies for treatment and prevention of multiple diseases; and 3) development of sensitive tools for early and definitive diagnosis, disease staging, and identification of at-risk individuals. Through a wealth of collaborative programs outlined above, NIH-supported scientists are vigorously pursuing these goals.

IMMUNE TOLERANCE

Mrs. Lowey: Dr. Fauci, in your testimony, you talk about "immune tolerance induction." Could you further explain this term to us, and what it means to immune-mediated diseases? How has the Immune Tolerance Network progressed? What is the promise of islet cell transplantation? How will this science benefit special populations?

Dr. Fauci: Immune tolerance utilizes specific approaches to selectively block or prevent harmful immune responses that are responsible for the rejection of transplanted organs, tissues, or cells as well as cause immune-mediated disorders, including autoimmune diseases, and asthma and allergic diseases. Immune tolerance goals include:

- For transplantation, to achieve long-term or permanent acceptance of transplanted organs, tissues, or cells. Through the induction and maintenance of immune tolerance, it may be possible to prevent rejection without the use of life-long immunosuppressive drugs, which globally suppress the immune system and cause severe side effects.

- For asthma and allergic diseases, to develop methods to block immune responses, especially responses to those allergens, such as ragweed, cockroach, and house dust mite, that cause or exacerbate these diseases.

- For autoimmune diseases, to identify therapeutic approaches to block those immune responses that cause the body to mistakenly attack its own organs, tissues or cells. The development of tolerizing regimens may help delay the progression of many autoimmune diseases and eliminate the need for potent immunosuppressive medications.

Since its inception in FY 1999, the Immune Tolerance Network (ITN) has established an international consortium of greater than 70 basic scientists and clinical investigators to test promising tolerogenic treatment regimens in four clinical areas: islet transplantation; kidney transplantation; autoimmune diseases; and asthma and allergic diseases. The ITN is now enrolling subjects in three phase I and II protocols, will begin enrolling in five additional protocols by the end of the third quarter in FY 2002, and 10 new protocols are under development. In addition, the ITN established a set of core laboratories to develop diagnostic assays to measure the induction, maintenance, and loss of tolerance in humans.

Examples of clinical trials conducted in the ITN include tolerance induction in the setting of:

- kidney transplantation
- pancreatic islet transplantation
- multiple sclerosis
- ragweed allergy
- cat allergy
- type 1 diabetes
- psoriatic arthritis

The goal of islet cell transplantation is to eliminate the need for daily insulin therapy through transplantation of islet cells to replace the insulin-producing pancreatic islets destroyed by type 1 diabetes. The ITN is currently conducting a multi-site international clinical trial seeking to replicate the results of the "Edmonton Protocol" for transplantation of islet cells. Completion of this study will provide an important platform for evaluating new tolerance induction therapies in islet transplantation. The ITN is planning two such additional trials using an antibody to the CD52 T cell antigen and an antibody to the CD3 T cell antigen. If successful, these new therapeutic approaches will greatly improve the quality of life of children and adults who suffer from the devastating effects of type 1, or juvenile onset, diabetes.

Transplantation: the development of new approaches to induce tolerance to transplanted solid organs, tissues, or cells may lead to substantial improvement in the quality of life for transplant recipients, especially African Americans who suffer from a high rate of kidney failure. Similarly, the development of these new therapeutic approaches will benefit children in need of transplants, improving long-term graft survival. Graft survival now averages approximately 10 years, and, with current therapies, the average pediatric transplant recipient requires four transplants during his or her lifetime.

Asthma: Asthma disproportionately affects African Americans, particularly children living in inner cities. Despite the availability of proven therapies and new agents in development, even the most effective therapeutics have limitations. The most promising therapeutic approaches are to develop new methods to inhibit allergic immune responses or induce tolerance to allergens. The development of new tolerizing regimens will greatly benefit those populations most severely affected by these diseases.

Autoimmune diseases: The development of tolerizing regimens may help delay the progression of many autoimmune diseases, which disproportionately afflict women. Several autoimmune diseases, including systemic lupus erythematosus and scleroderma, are highly prevalent among African American women. Type 1 diabetes disproportionately affects young children who would benefit enormously from tolerizing therapies that either delay disease progression or prevent disease onset.

INFLAMMATORY BOWEL DISEASE

Mrs. Lowey: Dr. Spiegel, I want to thank you for your interest and leadership in the area of IBD research. I understand that the new deputy director in NIDDK's Digestive Diseases and Nutrition Division is a leading IBD researcher. Could you give us an update on NIDDK's IBD research? Has NIDDK continued to partner with the IBD community in this area?

Dr. Spiegel: The NIDDK supports a broad and vigorous basic and clinical research program directed towards elucidating the causes of IBD and translating fundamental discoveries into better medical care for patients. The Institute funded two new multi-center clinical trials on IBD related problems, and multiple projects directed at IBD are under way in different NIDDK-funded Digestive Diseases Research Centers. In 2001, NIDDK-funded investigators identified the first susceptibility gene for Crohn's disease, Nod2, and in FY2002 the NIDDK will fund a consortium of IBD geneticists to accelerate the pace of discovery of the genetic basis of IBD, as well as to continue basic research to study the Nod2 gene. The NIDDK also co-sponsored an initiative led by NIAID to fund investigators in FY2002 to study potential infectious causes of IBD. In order to ensure a continuing pipeline of young investigators for the future, the NIDDK vigorously supports research training and research career development programs, which include young scientists interested in IBD research.

The NIDDK has worked in close harmony with the community of IBD clinical and basic investigators, and with the lay community, through fruitful collaborations with organizations such as the American Gastroenterological Association, the American Association of Immunologists, the Society for Mucosal Immunology, and the Crohn's and Colitis Foundation of America. These interactions promote the exchange of ideas about emerging research opportunities and facilitate rapid dissemination of new knowledge. The NIDDK also takes a strong role in maintaining an active dialogue among the other NIH institutes and centers with research interests related to IBD, such as NIAID, NCI, and NICHD. These interactions are facilitated by the Digestive Diseases Interagency Coordinating Committee, which the NIDDK chairs.

INTERSTITIAL CYSTITIS

Mrs. Lowey: Dr. Spiegel, NIDDK has made great progress in research on Interstitial Cystitis (IC). However, we still have not identified the etiology or understand the pathogenesis of IC. What is the next step in IC research at NIDDK? I understand that funding for IC research has decreased in the past two years - will that trend continue?

Dr. Spiegel: The NIDDK continues to support a multi-faceted approach to interstitial cystitis (IC) research. The question of immediate management of the complex array of symptoms suffered by patients with IC is being tackled by the NIDDK's Interstitial Cystitis Clinical Trials Group, which is currently running two clinical trials with different approaches to IC treatment. One trial is comparing combinations of oral medications for the most effective relief of symptoms, while the other is testing the efficacy of a therapeutic bladder wash to relieve pelvic pain and frequent urination.

To facilitate the identification and treatment of all persons with IC, and to gain knowledge on the full range of risk factors and clinical symptoms, awards have been made to study the epidemiology of IC, specifically broadening the surveyed population. The recently funded "Urologic Diseases in America," a retrospective study and compendium of statistics on urologic health care and disease prevalence, will also assist researchers in identifying individuals with IC and learning more about the burdens of this disease.

Research on management of the debilitating pain suffered by patients with IC will also be supported through collaborative efforts with other disease experts well-versed in pain management – such as those familiar with irritable bowel syndrome – as was recommended at the recent meeting entitled "Bladder and Interstitial Cystitis: Progress and Future Directions." This meeting was co-sponsored by the NIDDK and the Interstitial Cystitis Association.

Understanding the underlying causes of IC, however, remains at the top of the list of research priorities. At the moment, the most promising research avenues for IC lie in a better understanding of normal bladder physiology and of the pain pathways that are affected in IC. The recent identification of an anti-proliferative factor produced by the bladder and found only in the urine of IC patients has already provided clues into both the pathogenesis of the disease and to normal bladder function. The discovery has also generated many new research questions for pursuit. New findings about the pain pathways in the bladder have sparked intense investigation. Researchers are eager to investigate how the perturbation of these pathways releases chemicals which may, in turn, cause the altered bladder function observed in IC.

The NIDDK recently established the Bladder Research Progress Review Group (PRG). This group of external scientific experts met last summer in order to draw up a map for future research directions in bladder disease, including IC. The PRG made scientific recommendations on high-priority research areas for IC such as etiology and pathogenesis. These recommendations will be invaluable in aiding the NIDDK and its National Advisory Council to determine the best means possible to support this research. In addition, because the etiology and pathogenesis of interstitial cystitis are still unknown, the NIDDK's continued support of basic research on the structure and functioning of the bladder also provides a crucial framework for accumulating a knowledge base from which IC-specific research will surely benefit.

NIDDK funding for IC-related research has actually increased from $10.3 million in fiscal year (FY) 1999 to $12.4 million in FY 2001. The estimated level of funding for FY 2002 is $14.3 million, which is a 15.8 percent increase over FY 2001. Studies supported with these funds include clinical trials of IC therapies and research exploring the basic mechanisms of bladder disease, including bladder dysfunction, and possible underlying causes of IC. In response to the forthcoming scientific recommendations from the PRG, we expect to expand our portfolio of IC-related research projects.

INTERSTITIAL CYSTITIS

Mrs. Lowey: Previous research on IC led to the discovery of a protein unique to IC patients, which inhibits the growth of the bladder lining. Do you think that funding for IC-specific research like this will enhance our understanding of basic bladder function?

Dr. Spiegel: Yes. The identification of the anti-proliferative factor (APF) in the urine of interstitial cystitis (IC) patients, to which you refer, is important both for understanding the mechanisms and possibly the cause of IC, and for understanding normal bladder function. The effects of both normal and excessive levels of APF made by bladder cells are under active investigation. Research results demonstrating the ability of the APF to inhibit growth of the bladder lining are in peer-review for publication. We believe the results are promising, and we look forward to their

replication by other groups. IC thus provides one important window through which to view bladder function and dysfunction, and the NIDDK will continue to support basic research on IC.

At the same time, I would emphasize that it is important for the NIDDK to maintain a broad portfolio in basic bladder research, because multiple approaches to understanding bladder function could possibly provide not only general information, but also important insights or therapies for IC as well. For example, recent NIDDK-supported studies characterizing proteins lining the bladder have elucidated the protective function of these proteins. These studies have also provided insights regarding the types of bladder dysfunction that may result when these proteins are not properly made or are malfunctioning, thereby leaving the bladder cells underneath them open to damage from urine. Funded in response to the NIDDK solicitation, "Innovative Research Approaches to Basic Bladder Biology and the Painful Bladder Syndrome," this type of research is broader in scope than IC-specific studies, but may well have important implications for understanding different ways in which the bladder wall becomes damaged in disease. Its relevance to IC is therefore significant.

PREVENTION OF TYPE 1 DIABETES IN CHILDREN

Mrs. Lowey: I understand that there are several significant research studies with early promising results, focusing on the prevention of juvenile diabetes in children. What is the status of these studies?

Dr. Spiegel: We are very encouraged by recent studies indicating that it may be possible to modulate the immune system in ways to prevent or delay the onset of type 1 diabetes. The NIDDK is supporting ongoing trials to test these innovative research approaches and is also framing new initiatives to move this line of research forward as quickly as possible. The NIDDK has just launched a critically important new research program, the Type 1 Diabetes TrialNet, which was recommended by the congressionally established Diabetes Research Working Group. This TrialNet is funding a consortium of clinical centers and core support facilities to enable rapid, preliminary testing of emerging therapeutic strategies such as new ideas for immunoprevention. Strategies that appear promising in animal models will first be studied in patients with new onset diabetes to determine whether they can preserve residual pancreatic beta cell function and insulin production that makes control of diabetes easier. Those that prove most promising can then be moved quickly into larger-scale prevention trials in relatives of patients with type 1 diabetes who show evidence of damage to the insulin producing beta cells but do not yet have diabetes. A number of agents are under consideration for protocol development for both types of trials. There are several agents for which limited trials in small numbers of patients with new onset diabetes have suggested possible benefit and others for which animal data appear encouraging. The Type 1 Diabetes TrialNet will conduct trials jointly with the Immune Tolerance Network, which is studying a number of autoimmune disorders in addition to type 1 diabetes and is developing state-of-the-art assays to measure immune function.

The Type 1 Diabetes TrialNet is also completing a major multicenter trial currently under way to prevent type 1 diabetes. The objective of this trial, the Diabetes Prevention Trial for Type 1 Diabetes (DPT-1), is to determine if type 1 diabetes can be prevented through the administration of oral insulin in individuals considered to be at moderate risk with a 25 to 50 percent chance of developing diabetes over five years. In a recently completely trial in higher risk subjects who had already lost significant beta cell function, researchers have found that low-dose insulin injections do not delay or prevent diabetes. However, that trial showed that it is possible to accurately identify a high risk group of individuals and taught us a great deal about type 1 diabetes that will be useful for future trials. The ongoing oral insulin study is spearheaded by the NIDDK and supported by the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development, the National Center for Research Resources, the American Diabetes Association, and the Juvenile Diabetes Research Foundation International.

A major trial of prevention of type 1 diabetes in newborns who were found by genetic testing to be at high risk of type 1 diabetes is just beginning in the U.S., Canada and Europe. This trial will compare conventional milk-based formula to a milk-free formula to determine whether cow's milk plays a role in the development of type 1 diabetes. Another ongoing trial is studying whether nicotinamide can delay or prevent the development of type 1 diabetes in people at genetically high risk because a family member is already affected by the disease. This trial, the European Nicotinamide Diabetes Intervention Trial (ENDIT), is expected to be completed in 2003.

RECOUPMENT OF FEDERAL RESEARCH FUNDING

Ms. DeLauro: I understand that your 2003 budget request essentially doubles NIH's budget from its 1998 level. As you know I am a tremendous proponent of NIH research, however, I am concerned that, with this increase, not enough is being done to ensure that taxpayers interests are protected. We are investing in research that pharmaceutical companies use to make millions of dollars, and I am concerned that none of those profits are being recouped. We need to ensure that we get the most out of our federally funded research, so that large companies do not walk away with enormous profits from the hard work of others.

Can you outline for me essentially how basic research we fund at NIH leads to the creation of new drugs?

Dr. Kirschstein: There is no standard pattern or process for the development of discoveries from basic research. New discoveries may arise out of a large research project but often are ancillary to the main objective of the research. The findings can come from working around obstacles or through serendipitous discovery.

Most basic research discoveries are early-stage including proofs of concept, mechanisms of action, and basic interactions. They can include new compounds or chemicals. However, these discoveries require further research and development to demonstrate proof of principle and bring them to practical applicability.

We should make it clear that the NIH is not in the drug development business. We do not develop new therapeutics and simply hand them over to companies to manufacture and distribute. The NIH needs partners, licensees, to invest significant resources to conduct the further development required. This is a high risk venture for those who wish to pursue the development of these technologies.

Typically, technologies need to be further developed with the combination of other technologies to eventually create a product that can have the anticipated effect without side effects that would deter their use. That process of development of new products is long and expensive. It can takes years of development and many of these promising new discoveries fail to become efficacious and safe drugs.

Ms. DeLauro: Does NIH have a mechanism for recouping this funding? If so, how much?

Dr. Kirschstein: The NIH licenses technologies that originate from laboratories at the NIH. In exchange for licenses, the NIH receives royalty income which includes payments even before a technology comes to the marketplace. If and when an NIH technology becomes a part of a product that reaches the market, the NIH receives a portion of the sales as royalty income. By law, the income is used to provide inventors with a share of the royalties, pay for patent and other technology transfer related costs,

with most of the funds being returned to the laboratory to support further research. Last year, the NIH generated more than $46 million in royalty income. Over the past 7 years, we have generated more than $260 million in royalty income. The last report from the Department of Commerce indicated that the NIH is responsible for two-thirds of the royalty income generated by the entire federal government.

Recipients of NIH funds operate in essentially the same manner as the internal NIH inventors. They license technologies for further research and development and receive royalty income that is used in a manner similar to that used by the NIH. The NIH does not receive a share of income generated by recipients from licensing of their government-funded discoveries.

Ms. DeLauro: Particularly in light of the biotechnology revolution, would you support a more in depth study which would analyze how NIH's research money results in a new drug? For example, this study might look at the various organizations involved in the process, how they interact, who incurs the risk in drug development and how much, and who makes the profit. This analysis could serve as a baseline for further study into how much the federal government recoups its research funding, and as a map for where improvements can be made.

Dr. Kirschstein: We believe that a recent report may address a number of the questions you have raised. The NIH submitted a report to the Congress in July 2001 in response to its request in Congressional Conference Report for a plan to ensure that taxpayers' interests are protected. That report concluded that the taxpayers have greatly benefitted from new diagnostic, therapeutic and vaccine products that were developed and have extended life and improved health. In addition, the study cites a report by the Congressional Joint Economic Committee issued in May, 2000 entitled "The Benefits of Medical Research and the Role of the NIH." That report concluded that the taxpayer receives the economic benefit of a return of $15 dollars for every $1 invested in the NIH. A copy of the report has been provided to the Committee and is available on the NIH website, http://www.nih.gov/news.

The report does not provide specific information on the amount of risk and profit of the various parties to the drug development process. That type of study would require the full cooperation of industry and access to business confidential information that is not available to the NIH.

MICROBICIDES

Ms. DeLauro: Dr. Fauci, given what we now know about the wiliness of HIV, the challenges of vaccine development, and the difficulties that women, especially, have to protect themselves from infection, it seems that research on microbicides should be a very important part of NIH's portfolio. I know that NIAID has gradually been increasing its funding for this area. Dr. Fauci, the committee wants to congratulate you for your efforts to increase the level of resources for microbicide research and development.

How many staff are currently working exclusively on microbicides, and what changes are you making to accommodate the needs of your expanding investment in this area?

Dr. Fauci: Intramurally, we currently devote four full-time equivalent positions to topical microbicide research with plans to hire additional staff including a medical officer and behavioral scientist who would be predominantly working on topical microbicide development. Microbicide research is multi-disciplinary in nature and in addition to those specifically devoted to topical microbicides, staff throughout the Division of AIDS continue to make substantial contributions to our research efforts in this area. For example, it is particularly important, to utilize staff with broad expertise in the process of drug discovery. This is because the screening of potentially useful topical microbicides can be pathogen-specific (based on the different properties of the sexually transmitted infectious agent) and requires knowledge about drug targets for both HIV and other sexually transmitted diseases. Similarly, staff with expertise in preclinical toxicology help ensure that critical testing occurs, and medical officers facilitate collaboration with investigators and industry in the design, management, and analysis of clinical trials.

In combination with our staff expansion, we are starting a major research initiative in FY 2003 that seeks to expand the number and scope of candidate microbicides in the "pipeline" to an advanced development stage and early human clinical trials; encourage a combination of approaches to prevent attachment of HIV at multiple points of entry; attract the private sector to microbicide development; and fill fundamental and epidemiological gaps critical to the through evaluation of microbicides in clinical trials.

Ms. DeLauro: We know that a number of candidate microbicides, are being developed that appear safer and less irritating than earlier products and work by a variety of different mechanisms. How much money do you think will be needed to bring these products through clinical testing?

Dr. Fauci: It is difficult to estimate the amount of financial support that would be needed to bring current and future candidates through clinical trials. Our estimate is that to take one candidate topical microbicide from preclinical testing through all phases of clinical evaluation (from early safety studies to efficacy and effectiveness trials) would be between $60 and $80 million.

Because any individual candidate can be formulated in different ways that may affect acceptability as well as effectiveness, the full costs of development may well exceed this estimate. In addition, the most effective products may be ones that combine multiple active agents and, again, the cost for development would exceed that of a single agent because of the need to repeat for both single agents and the combination of many of the steps involved in preclinical and clinical testing.

Ms. DeLauro: We have heard wonderful things about the vaccine program that has been created within the Division of AIDS. Specifically, that the Program is focusing on a product development strategy and has devoted significant dedicated staff to this area. Given considerable similarities between vaccines and microbicides, in that public sector support for research in this area is crucial for progress, has NIAID thought about a similar approach for microbicides?

Dr. Fauci: Yes. The Division of AIDS is in the process of replicating several programs for topical microbicide research that have been effective in advancing HIV vaccine research. For example, we recently established the Integrated Preclinical/Clinical Program for HIV Topical Microbicides, which is modeled after a similar program for vaccines. The program will support translational, iterative research, whereby results from pilot clinical trials will be used to optimize product development. Another highly successful model is that of the Innovation Grant Program, which has supported research on novel HIV vaccine concepts. We have created a similar program that encompasses topical microbicide development and anticipate making the first awards in early FY03.

OVARIAN CANCER

Ms. DeLauro: As you know, I have a deeply personal interest in ovarian cancer. I appreciate all the work NIH has done to support ovarian cancer research, such as including ovarian cancer in the SPORE program. As you know, a study published in February found a simple blood test that seems to be able to detect ovarian cancer at an early stage, when treatment would be most effective. I don't need to tell you what an incredible breakthrough this would be, since right now there is no reliable screening method for ovarian cancer. Can you give us your thoughts on this research? Also, can you please update us on where NIH is in its various ovarian cancer projects, whether you believe there are other promising breakthroughs on the horizon, and how much you plan to invest overall this year?

Dr. von Eschenbach: Last month, the NCI, along with the Food and Drug Administration (FDA) reported that patterns of proteins found in patients' blood serum may reflect the presence of disease. In the study, scientists used serum proteins to detect ovarian cancer, even at early stages. They report that this new diagnostic concept is potentially applicable to any type of disease.

Using a test that can be completed in 30 minutes using blood obtained from a finger stick, researchers were able to differentiate between serum samples taken from patients with ovarian cancer and those from unaffected individuals. The research, a joint effort between the FDA, NCI and Correlogic Systems Inc., unites two exciting disciplines: proteomics - the study of the proteins inside cells - and artificial intelligence computer programs.

The diagnostic test relied on software that was able to detect patterns of key proteins in the blood. Using a sophisticated artificial intelligence computer program developed by Correlogic, scientists were able to "train" the computer to distinguish between patterns of small proteins found in the blood of cancer patients vs. control samples. The artificial intelligence program identified a pattern consisting of only a handful of proteins, among thousands, that could be used to distinguish between women with ovarian cancer and women with non-cancerous conditions. The idea that rather than a single biomarker, an entire pattern of proteins contains important diagnostic information, is an exciting new paradigm.

An important finding was the ability to correctly identify, in a small sample of patients, all stage I ovarian cancer cases. Currently, more than 80 percent of ovarian cancer patients are diagnosed at a late clinical stage and have a 20 percent or less chance of survival at 5 years. In contrast, the 20 percent of women diagnosed with early-stage disease have an excellent prognosis, with over 95 percent alive at 5 years after diagnosis. The results of this study indicate that proteomic technology may help clinicians diagnose the disease much earlier than current methods.

Further study is needed to confirm the sensitivity and accuracy of this technique as a diagnostic tool. We hope that by combining the proteomic approach with other methods of ovarian cancer diagnosis, such as ultrasound, its accuracy can be further improved. We must validate the promise of these results in a large, multi-institutional trial. Such trials are underway at the NCI, evaluating proteomics both alone and in combination with current screening methods for ovarian cancer.

There are a variety of different ovarian cancer research projects underway. Currently, we have four funded Ovarian Cancer SPOREs, who are conducting research aimed at improving current methods of screening for ovarian cancer. Activities include identifying, characterizing, and validating a number of biological markers that could be utilized in combination with CA-125 to improve the detection of ovarian cancer, especially stage I disease. While the technology being utilized to identify these markers differs from those employed by NCI intramural investigators, the underlying principle is the same. All are aimed at identifying a panel of markers (vs. a single marker) that together will provide greater power to identify ovarian cancer cells in the blood. This type of effort requires sophisticated statistical input; focused upon the development of novel statistical models or algorithms.

Several of the SPOREs are collaborating to characterize surgically removed ovaries from patients at high risk for ovarian cancer in an attempt to identify genetic lesions or expression patterns in these cells that correlate with malignant progression. The intent here is similar to the one above, to identify a diagnostic marker(s) that can help clinicians detect cancer at an early stage.

All four SPOREs have formed a collaboration with the NCI Cancer Genetics Network (CGN) to perform a pilot screening trial on women at high risk for ovarian cancer. This trial involves quarterly monitoring of CA-125 levels and the performance of annual transvaginal sonography (TVS) exams. One of the primary goals of this study is to identify high risk women and move towards providing them with better screening, prevention, and treatment options.

Another important goal is to obtain serial specimen samples from these women that can be utilized to test and validate new biomarkers for ovarian cancer. Currently, the SPORE scientists are also developing a chemoprevention arm for this study based on their knowledge of ongoing chemoprevention trials at three of the SPOREs. The current chemoprevention trials in these SPOREs involve the administration of a COX-2 inhibitor, progestin, or retinoid.

A number of novel therapeutics have also been developed within the SPOREs. Most of them are targeted therapies based upon a biological aspect of ovarian cancer and, as such, are potentially much less toxic than conventional chemotherapies. Many are either in the final stages of pre-clinical development or have moved into early phase (I/II) trials.

In addition NCI's Prostate Lung Colorectal Ovarian Cancer (PLCO) trial, which recently completed accrual of 146,000 men and women, included an evaluation of serum CA 125 and ultrasound as screens for ovarian cancer. Investigators associated with the PLCO study obtained early results by analyzing the baseline transvaginal ultrasound examination results for 20,000 postmenopausal women. In this group of asymptomatic women, ovarian abnormalities identified on ultrasound were assessed for their potential to be ovarian cancer precursors by correlating them with known ovarian cancer risk factors. Several strong risk factors for ovarian cancer such as a family history of ovarian cancer or breast and ovarian cancer and long term oral contraceptive use were not associated with the presence of complex cysts, simple cysts, bilateral cysts, or all abnormalities combined. These observations suggest that the abnormalities found on ultrasound were not immediate precursors of ovarian cancer.

The Ovarian Cancer Early Detection Proteomics Initiative is a component of the Clinical Proteomics Program, an inter-agency collaboration between the Center for Cancer Research, NCI, and the Center for Biologics Evaluation and Research, FDA. The mission of this new initiative is to credential and validate a new proteomics/bioinformatics technology that has preliminarily demonstrated high sensitivity, specificity, and positive predictive value for the discrimination of the presence of ovarian cancer, including stage I, from benign ovarian disease and unaffected women. This test, using less than a drop of serum, involves making a protein fingerprint of 15,500 proteins in the low molecular weight protein range. This fingerprint is then analyzed using a pre-trained multi-dimensional pattern discovery

algorithm. This system correctly identified all cancers, including all stage I cancers in the test sets. This approach is easily applied to point of care and it is envisioned that it can be applied broadly through secure web links.

A second initiative in the Ovarian Cancer Project of the Clinical Proteomics Program, NCI/FDA, is global unbiased protein target and marker discovery directly from patient specimens. This project applies state of the art proteomic technology to protein pattern analysis, protein isolation, and micro-sequencing for identification. This project has identified and attributed selectively to invasive ovarian cancer over a dozen new or known proteins. Ongoing work is validating these findings for use as new molecular treatment and/or imaging targets.

In February 2001 the NCI convened a Gynecologic Cancer Progress Review Group (PRG) to identify and prioritize those areas of research that held the best promise for advancing progress in ovarian, cervical, and endometrial cancer. A roundtable meeting of approximately 120 experts in related fields was held in June 2001. The recommendations of the PRG were officially accepted by the NCI in December 2001. Several of the highest priorities identified by the PRG concerned ovarian cancer. These included the elaboration of a specimen resource, the identification of precursor lesions, markers of risk and early detection, molecular disease classifications, prognostic indications, and new targets for prevention and treatment, as well as efforts to eliminate disparities in care and improve patients' quality of life. As with PRGs in other cancer sites, the NCI has convened a trans-institute working group to implement these recommendations.

Overall, the NCI plans to invest $88.6 million on ovarian cancer research in FY 2002 and $102.1 million in FY 2003. Across all of NIH, spending on ovarian cancer research is expected to be $104.0 million in FY 2002 and $118.9 million in FY 2003.

IMPACT OF FUNDING INCREASE ON THE OFFICE OF WOMEN'S HEALTH RESEARCH

Ms. DeLauro: We have all been proud to see the NIH budget double over 5 years. What has the impact of these large incremental funding increases been on the Office of Women's Health Research? In your opinion, has the Office seen a proportional increase in its capacity to achieve its mission in being the center point for research on women's health?

Dr. Kirschstein: The capacity of the Office of Research on Women's Health (ORWH) to achieve its mission of being the center point for research on women's health is not necessarily dependent on the level of its budget relative to the rest of NIH's budget. As one of its tools, ORWH is an active partner with the NIH institutes and centers (ICs) in supporting research to address women's health issues and to promote the identification of grants that represent scientific opportunities. By providing partial or total support for grant awards, ORWH enables the ICs, and therefore NIH, to fund

additional research in women's health or gender comparison studies. The ORWH has established a successful collaboration with the ICs that facilitates this process and that has resulted in important contributions to expanding women's health research, promoting careers of promising women researchers, and supporting career development of men and women as investigators in women's health. In FY 2002, ORWH received a substantial increase of nearly 70% in its budget to expand these collaborations.

With the FY 2002 increase in funding, ORWH has been able to place emphasis on Interdisciplinary Initiatives including the reissuance of the RFA for Building Interdisciplinary Research Careers in Women's Health (BIRCWH) II and developing an RFA for the new Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs) program to focus on interdisciplinary research .

BIRCWH II

ORWH reissued the BIRCWH RFA in FY 2002. The goal of this initiative is to promote the performance of research and transfer of findings that are relevant to women's health, including sex/gender similarities or differences in biology, health or disease. Each BIRCWH progam will accomplish this by bridging advanced training with research independence, as well as bridging professions, scientific disciplines, and/or areas of interest. BIRCWH II is supported by ORWH, with additional support from 7 NIH ICs, the Office of Dietary Supplements, and the Agency for Healthcare Research and Quality (AHRQ).

SCORs

The ORWH has also developed a RFA in FY 2002 (RFA-OD-02-002), Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs) to provide new opportunities for interdisciplinary approaches to advancing studies on how sex and gender factors affect women's health. Each SCOR will develop research bridging basic and clinical research on sex/gender factors underlying a priority health issue. The SCOR program will complement other NIH and Federally supported programs addressing women's health issues. This new program embodies many of the concepts set forth in the Institute of Medicine report, *Exploring the Biological Contributions to Human Health: Does Sex Matter?*

The objective of the SCOR program is to expedite interdisciplinary development and application of new knowledge to human diseases, to learn more about the etiology of these diseases, and to foster improved approaches to treatment and/or prevention. Awards will be made in the Fall of FY 2002.

In addition to the ORWH, the SCORs program is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Child Health and Human Development, the National Institute of Dental and Craniofacial Research, the National Institute of Diabetes and Digestive and Kidney Diseases, the

National Institute on Drug Abuse, the National Institute of Environmental Health Sciences, the National Institute of Mental Health, and the Food and Drug Administration.

COORDINATION AMONG WOMEN'S HEALTH OFFICES

Ms. DeLauro: How do you coordinate with the offices of women's health at other agencies, such as the FDA, HHS, CDC and others? In your opinion, is this coordination sufficient to see that the progress made at NIH is translated to other agencies (and vice versa) in order to make the broadest and most effective impact on the overall state of women's health?

Dr. Kirschstein: The NIH Office of Research on Women's Health (ORWH) interacts, collaborates, and communicates regularly with the offices of women's health across the U.S. Department of Health and Human Services (DHHS). These interactions and communications occur through a variety of channels: (a) participation in regularly scheduled monthly meetings of the DHHS Coordinating Committee on Women's Health; (b) attendance at jointly sponsored scientific and programmatic meetings; (c) participation in special projects sponsored by several Federal agencies; (d) cross-agency development and support for women's health research training; (e) formal written communication; and (f) attendance at meetings of the directors of the offices of women's health. Such interactions, collaborations, and communications include the following.

The DHHS Coordinating Committee on Women's Health is co-chaired by Dr. Wanda K. Jones, Director of the DHHS Office on Women's Health (OWH). The DHHS Coordinating Committee was established to advise the Assistant Secretary for Health and the Deputy Assistant Secretary for Health (Women's Health) on current and planned activities across the Department relating to women's health. The Committee's members include senior-level representatives from each of the Federal agencies and offices within the DHHS. Dr. Vivian W. Pinn represents the ORWH at these meetings, and many other ORWH staff participate in department-wide committees, meetings and workshops.

Over the years, ORWH has enjoyed tremendous support from sister offices throughout the DHHS. The ORWH held a series of national meetings to examine progress and determine continuing gaps in knowledge concerning women's health research in order to develop an agenda for future research. Staff representing women's health offices and programs throughout the DHHS participated and made valuable contributions to the resulting six-volume report, *Agenda for Research on Women's Health for the 21st Century*. Whenever the ORWH sponsors a meeting or conference, representatives of each of the DHHS offices of women's health are invited to participate. The collaborative and cooperative relationship among the DHHS offices dedicated to improving women's health is shown in the article, "The NIH Office of Research on

Women's Health and Its DHHS Partners: Meeting Challenges in Women's Health" (*Journal of the American Medical Women's Association.* 54, no. 1 [1999]: 15-19), in which the ORWH invited all other DHHS offices to describe their salient programs and activities.

There have been many research services, educational conferences, and workshops that have benefitted from the collaboration of two or more women's health offices of the DHHS. For example, the NIH/ORWH career development initiative, Building Interdisciplinary Research Careers in Women's Health (BIRCWH), is supported by nine NIH institutes and by the Agency for Healthcare Research and Quality (AHRQ). The AHRQ Senior Advisor on Women's health was instrumental in bringing about this collaboration, which allowed for a broader programmatic perspective.

Two new research projects have been recently initiated in collaboration with the AHRQ. The first reviews Gender Differences in Cardiac Care. This Collaborative Federal Agency Review is a Phase II project which builds upon the findings and recommendations from the initial study that identified the scientific evidence and basis relating to sex and gender differences in coronary heart disease, its diagnosis and subsequent treatment. The second project, also with the AHRQ, will generate an Evidence-Based Report on the Use of Uterine Artery Embolization (UAE) Procedures and Related Surgical Procedures for Treatment of Conditions That Can Lead to Hysterectomy. The ORWH and the AHRQ will develop this report on uterine artery embolization procedures and related surgical and non-surgical procedures for treatment of conditions that can lead to hysterectomy. The NIH/ORWH will work with the AHRQ to provide guidance, as appropriate to the Evidence-based Practice Centers (EPCs) conducting this review.

As another example of collaboration, the Food and Drug Administration has joined with NIH as a cosponsor to support the initiative for Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs).

In summary, the Directors and staff members of all the DHHS offices concerned with women's health enjoy excellent interactive communication and support for our common goals. Resources and program coordination are greatly enhanced and facilitated by the DHHS Office on Women's Health and the DHHS Coordinating Committee on Women's Health, and NIH will continue to support these efforts.

DIABETES RESEARCH FUNDING

Mr. Jackson: The 1999 Congressionally mandated Diabetes Research Working Group recommended that diabetes research at NIH receive $1.5 billion in fiscal year 2003. The President's fiscal year 2003 budget provides $845,000 to diabetes research at NIH. What plans do you have to ensure that the research opportunities identified in this report are funded?

Dr. Spiegel: Since issuance of the Diabetes Research Working Group's Strategic Plan in 1999, we have been able to launch multiple new and exciting diabetes research initiatives – and to sustain and expand ongoing efforts – with the funding increases provided to the NIH. Diabetes research spans the many institutes and centers of the NIH and is benefitting from fruitful scientific and funding collaborations, both among NIH components, and with diabetes voluntary groups and industry. Trans-NIH diabetes research funding increased from a level of $458 million in FY 1999, to $540 million in FY 2000, and to $688 million in FY 2001, with estimates for FY 2002 and FY 2003 projected to be $781 million and $845 million, respectively.

In developing the trans-NIH diabetes research portfolio over these years, we have been largely guided by the scientific recommendations of the Diabetes Research Working Group's 1999 Strategic Plan. Thus, we have placed special emphasis on the five areas identified by the DRWG as "extraordinary opportunities"– genetics, autoimmunity and the beta cell, cell signaling and cell regulation, obesity, and clinical research and trials. Within this framework, we have developed major initiatives in consultation with our National Advisory Council, and with leading experts from the diabetes community from whom we have solicited scientific advice at workshops and conferences, and through *ad hoc* program planning meetings. The NIDDK has also mobilized and catalyzed diabetes research across the NIH through its chairmanship of the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC), which includes representation from each relevant institute and center of the NIH, as well as representation from the CDC and FDA. This is an excellent mechanism for focusing NIH-wide attention on special research challenges in diabetes, including the increased rates of type 2 diabetes in children and the disproportionately severe burden that diabetes places on minority groups, such as Native Americans and African Americans. The DMICC is also a mechanism for framing collaborative initiatives among the NIH institutes and centers with respect to the complications of diabetes, such as eye, kidney, nerve and heart complications.

Several initiatives undertaken in response to scientific recommendations of the DRWG involve establishment of research consortia to ensure that opportunities identified by the DRWG are pursued in a comprehensive and coordinated manner. For example, large multi-disciplinary and multi-center teams of basic researchers have been assembled to investigate the genetics of the major forms of diabetes and its complications and to understand at the molecular level how the insulin-producing beta cells in the pancreas develop and function. Networks of clinical investigators have been

established to conduct trials of interventions to prevent type 1 and type 2 diabetes in children. We have also endeavored to develop critical research resources such as animal models of diabetes, expand our diabetes research centers, and apply cutting-edge technologies to diabetes research. These technologies range from genomics to proteomics to new imaging modalities. Particularly important, in light of new findings from clinical trials, is dissemination of research results and expansion of translational research to develop new methods of encouraging practitioners to implement interventions proven beneficial in clinical trials.

Using all the approaches I have just described, the NIDDK will continue to provide strong leadership across the NIH to realize the scientific goals and objectives delineated by the DRWG, within the context of available budgetary resources and programmatic needs. We will mobilize broad support for the continuation of ongoing initiatives and for the development of new efforts to capitalize not only on the opportunities that were identified by the DRWG in 1999, but also on new opportunities that have since emerged.

HIGH BLOOD PRESSURE IN AFRICAN AMERICANS

Mr. Jackson: I am very concerned that the prevalence of high blood pressure in ~~African Americans in~~ the United States is among the highest in the world. As I understand it, compared with whites, African Americans develop high blood pressure earlier in life and their average blood pressures are much higher, which as you know is a major risk factor for heart disease and stroke. Please tell this Committee what NIH is doing to address this high blood pressure disparity in blacks?

Dr. Lenfant: The NHLBI supports extensive investigation into the causes of excess hypertension and its health consequences in African Americans, including the role of diet, obesity, genetics, stress, discrimination, lifestyle, and socioeconomic status. Studies exclusively involving African-American communities, such as the Jackson Heart Study, and others involving comparisons with other ethnic groups are examining the impact of hypertension on risk of heart attack, heart failure, stroke, cognitive impairment, and peripheral arterial disease. The key role of diet is under close investigation. Relationships between blood pressure and body weight, high sodium and alcohol intake, and low potassium intake are well established. An epidemiologic study called INTERMAP is examining the relationship between blood pressure and consumption of protein, amino acids, fats, cholesterol, carbohydrates, calcium, magnesium, antioxidants, fiber and caffeine. To understand both the genetic and environmental determinants of hypertension, the Institute supports collaborative community-based research comparing three geographically distinct populations of African origin from Nigeria, Jamaica, and the Chicago area.

The NHLBI has for many years made a large investment in research to evaluate interventions for prevention and treatment of hypertension, with an emphasis on acquiring results that are applicable to African Americans. Two recent landmark

controlled-feeding studies in adults, over 60% of whom were African Americans, demonstrated that substantial blood pressure reduction could be attained rapidly through the so-called DASH diet (an eating pattern high in fruits, vegetables, and low-fat dairy products and low in fat). The benefits of this regimen were somewhat greater in African Americans than whites, and were even more striking when sodium intake was also reduced. In the ongoing PREMIER trial, NHLBI-supported investigators are testing, in persons (60% of whom are African American) who themselves select what they eat each day, whether providing counseling for following the DASH diet is effective in lowering blood pressure, over and above the effects of weight loss, increased physical activity, reduced salt intake, and moderation of alcohol use.

With regard to pharmacologic treatment, the NHLBI-sponsored Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is studying over 42,000 patients (35% African American) to determine the best antihypertensive drug selection to prevent heart attack, stroke, and other cardiovascular disease (CVD) complications. When the ALLHAT results are reported later this year, physicians will be very much better informed about drug selection to achieve maximum benefit, given a patient's race and gender.

Since its inception, the National High Blood Pressure Education Program (NHBPEP) has been working to inform African Americans about the dangers of high blood pressure and encouraging them to have their blood pressure measured and to adhere to prescribed medication regimens. As a result, in part, of public service announcements, data indicate that African Americans are more likely to be aware of their high blood pressure than the general population. The NHBPEP has focused media efforts through activities such as HealthBeat Radio Network, which provides 30- and 60-second radio messages, many of which are designed to encourage African Americans to stay on their blood pressure medications. The NHBPEP also supported the development and distribution of a church guide, which was a planning tool for faith-based organizations to develop high blood-pressure screening and tracking programs. In cooperation with the International Society Hypertension in Blacks (ISHIB), the first Sunday in May was declared church high blood-pressure Sunday. Further, in an effort to reach younger men, a blood pressure planning kit was designed to develop screening and educational programs at sporting events. Many communities now routinely conduct hypertension screenings for men at high school football and basketball games and minor league baseball games. The NHBPEP has also produced and distributed educational pamphlets dealing with use of lower salt and lower fat ingredients in African American recipes. These recipes have been assembled into cookbooks which are used in many church and community-based programs. A community planning kit for high blood pressure month (May) has been available for state and local health agencies and voluntary hospital-based programs, to help them develop hypertension outreach, education, and screening programs, and to alert the media regarding the benefits of hypertension prevention and treatment, especially among African Americans. These

materials are used by many organizations to leverage the programs' reach, so that more Americans, especially African Americans, have their blood pressure measured, adopt a lifestyle to prevent hypertension, and get treatment as needed.

Although there have been major successes in disseminating science-based information, many communities have not been receiving all the benefits of scientific research results. To ensure that science-based information about CVD reaches people in local communities, particularly low-income and minority communities, the NHLBI funded six Enhanced Dissemination and Utilization Centers (EDUCs) in FY 01, and will fund up to eight additional EDUCs in FY 02. Their purpose is to plan, develop, implement, and evaluate well-defined, focused educational intervention strategies aimed at reducing the burden of CVD through changes in behaviors of health care providers, patients, and the general public related to the control of CVD and associated risk factors and the promotion of heart-healthy behaviors. Centers are currently located in low-income communities in Virginia, West Virginia, Arkansas, North Carolina, and Texas, and several of them target African Americans. In addition to these activities, the NHLBI is collaborating with the Baltimore City Cardiovascular Health Partnership, a community-based coalition, to develop science-based educational and training materials and to use these tools to stimulate the implementation of community-based activities to improve cardiovascular health of public housing development residents and staff.

PROSTATE CANCER RESEARCH

Mr. Jackson: In 1998, Congress recognized that prostate cancer research was under funded, especially efforts to conquer the disease in black communities, and it required NIH to submit a 5-year professional judgment budget to enhance efforts to beat this all-too quiet killer. Congress received that plan in June 1999, and is now asking NIH to provide an updated research plan for the next 5 years.

From 1999 through 2003, NIH said that it would invest more than $1.5 billion in prostate cancer research. Yet, in each of the last three years, NIH's actual investment has fallen short of its projections.

Can you explain this discrepancy between your stated goal in the 5-year plan, your budget requests and what has been actually spent? Why is this the case? How can we attract good researchers to the field if you are not fully funding your stated commitment? What assurances will we have for better accountability in FY 2003 and in the next 5- year plan?

Dr. von Eschenbach: The National Cancer Institute (NCI) allocates its budget across mechanisms and various diseases according to scientific opportunities based on peer review. For the NCI, Prostate cancer has long been a priority area for funding and scientific research. It has seen dramatic annual increases of funding [from FY 1998 to FY 1999 prostate funding increased 56%, from FY 1999 to FY 2000 prostate funding increased 50%, and from FY 2000 to FY 2001 prostate funding increased 27%].

As reflected in the table below, the NCI funding for prostate cancer has substantially increased in the past 5 years. In FY 2002 NCI estimates that it will spend $291,000,000 on prostate cancer research and $331,000,000 in FY 2003. Over the 5-year period from FY 1999 - 2003, NIH spending on prostate cancer research is expected to be greater than $1.5 billion.

NIH and NCI Funding of Prostate Cancer Research (dollars in thousands)

	1999	2000	2001	2002	2003	1999-2003
	Actual	Actual	Actual	Estimate	Estimate	Total
NCI alone	$135,704	$203,200	$258,000	$291,000	$331,000	$1,218,904
Total NIH	177,505	256,694	320,107	362,095	408,314	1,524,715

In addition, for FY 1999, 2000 and 2001, both the NCI and NIH actual funding for prostate cancer has been at least 95% of the amount that was submitted in the original 5-year professional judgment budget presented to Congress. As evidenced by these increases, the NCI has made significant inroads in expanding resources dedicated to prostate cancer research, as well as placed greater emphasis on the disparate incidence of prostate cancer in black men. The planning for prostate cancer funding, and for all funding, is an ongoing and fluid process. Recently, the NCI developed its Strategic Plan for Reducing Cancer-Related Health Disparities. This 5-year plan outlines NCI's intention to invest in research to explain social, cultural, environmental, biological, and behavioral determinants of prostate and all cancers, the interactions among them, and the mechanisms by which they contribute to disparities in cancer care and prevention. It is envisioned that this plan will be a rolling 5 year plan. It will be updated annually to report on discoveries and progress and to outline the vision for scientific opportunities for the next 5 years. Scientific discovery is impossible to predict, and giant breakthroughs such as the discovery of a gene can severely change our course of research.

The delays that concern Congress have been due to the difficulties incurred in launching new programs and expanding existing programs, however, NCI launched the program dedicated to partnerships and collaborations between Minority Serving Institutions (MSIs) and NCI-designated Cancer Centers in FY 2001. This is a complex program that reaches out to over 400 MSIs with the objectives of increasing the cancer research in MSIs, increasing the number of minority investigators engaged in cancer research and increasing research at NCI-designated Cancer Centers that is focused on minority health disparities. By the end of FY 2002, this Minority Institution/Cancer Center Partnership Program will be providing nearly $16 million of grant support, much of which is dedicated to prostate cancer in black men.

The efforts of cancer training have been expanded for minorities in all areas of career development. Last year, opportunities for minority scientists engaged in patient oriented research were initiated and are expected to expand significantly over the next 5 years and beyond. NCI is also supporting a new extramural loan repayment program in FY 2002. This NIH-wide program is designed to recruit and retain highly qualified health professionals as clinical investigators by offering partial repayment of student loan debt. It is our hope that this program will be another tool to continue feeding the pipeline of minority cancer researchers.

In addition, between FY 2000 and FY 2002, the NCI has expanded the number of prostate cancer Specialized Programs of Research Excellence (SPOREs) from 3 to 8, an increase of nearly $15 million dedicated to bench-to-bedside or translational research. The SPOREs have a dedicated career development component that is very flexible in that it can recruit either postdoctoral candidates or more experienced investigators who wish to change the direction of their research toward translational research objectives; prostate cancer SPOREs are training 10 to 20 investigators at any given moment, of which 1-3 are minorities, since each SPORE must have a plan in effect for recruiting minorities into its career development efforts. Interestingly, the power of SPOREs to recruit more minorities into translational research and develop projects that address minority health disparities is being magnified by the interactions of SPORE scientists through Comprehensive Minority Institution/Cancer Center Partnerships (MICCPs) noted above. For example, the Johns Hopkins prostate cancer SPORE scientists are very active in establishing collaborative projects with scientists at Howard University as part of the existing MICCP; to date, every project in the MICCP is training minority scientists and is dedicated to understanding prostate cancer in African Americans. The NCI believes that prostate cancer SPOREs will serve as platforms for more research that addresses the incidence and mortality disparities in blacks with prostate cancer as well as serving as research environments for training new black investigators.

As indicated above, prostate cancer research is a high priority for the NCI and the research portfolio in this area has and continues to show substantial growth. For example, 8 SPOREs focused on prostate cancer are in place.

NCI's planning for prostate cancer research is guided primarily by the 1998 recommendations of the Prostate Cancer Progress Review Group (PRG) presented in its report, *Defeating Prostate Cancer: Crucial Directions for Research.* At an implementation meeting with the PRG in January 1999, the NCI Director proposed a series of actions in response to the PRG recommendations. Subsequently, NCI prostate cancer activities increased substantially.

As envisioned in 1999, a process to report progress on research priorities identified by the Prostate Cancer PRG Report has been initiated. An internal working group of prostate cancer experts has been assembled and is in the process of choosing measures of progress, collecting data, and preparing a progress report. The measures of progress will range from the shorter term, such as increases in funded projects and

identification of resulting key scientific advances, to the longer term, such as developing new approaches to prevention and treatment. When the progress report is complete, a group of scientists, clinicians, and advocates, including some former Prostate Cancer PRG members, will meet to review this report and, if indicated, recommend adjustments to NCI strategies. NCI will use the results of this progress report review to adjust strategies for prostate cancer research as needed. This mechanism for reporting progress on prostate cancer research and assessing the need for any strategy adjustments will be helpful in both documenting NCI's past and current efforts, and guiding future research activities.

PROSTATE CANCER

Mr. Jackson: In its 1999 professional judgment budget, NCI identified six core areas to accelerate new treatments for prostate cancer patients, including targeted drug discovery based on the molecular mechanisms underlying the disease; improving classifications of tumors to improve the development of targeted drugs; developing new biomarkers to distinguish between aggressive and indolent prostate cancer; and enhancing NCI's SPORE, or specialized programs of research excellence, to facilitate translational research.

Enhancing early detection of aggressive vs. non-aggressive prostate cancer is crucial, but especially so in the African American community. African American men are much more likely to be diagnosed with advanced disease, in which treatment for prostate cancer is much more difficult and more likely to be unsuccessful. In 1999, you called for the establishment of specific prostate cancer initiatives to address this problem.

Are there any new programs in place as a result, and can you identify any successes?

Dr. von Eschenbach: NCI is supporting a variety of initiatives to develop resources that will aid efforts to identify the genetic factors that contribute to prostate cancer susceptibility. Each of the eight SPOREs is in the discovery phase of new potential biomarkers using cDNA and tissue microarray technologies. Through collaborative efforts, the prostate SPOREs have developed in the past year the necessary infrastructures to validate relevant biomarkers for prostate cancer using high throughput analysis and technologies that will ultimately bring into clinical practice new biomarkers for diagnosis, prognosis, and treatment.

In addition, the prostate SPOREs, are designing collaboratively tissue microarrays to address studies on special populations including African Americans, Hispanics, and Asian Americans. These multiethnic tissue microarrays will be used to test relevant biomarkers and compared with those found in the population at large.

NCI's SPOREs for prostate cancer and the International Consortium for Prostate Cancer Genetics (ICPCG) also are important vehicles for gene discovery research. The ICPCG, formed to address and overcome problems associated with prostate cancer susceptibility gene mapping and identification, is a large group including families from diverse ethnic and racial backgrounds. It is ideally suited to address questions pertinent to the molecular genetics and genetic epidemiology of prostate cancer. The ICPCG's collaborative infrastructure will make it possible to expeditiously pursue important issues, such as identifying the most important regions of the genome for prostate cancer, generating a comprehensive database to identify genes that are consistently associated with prostate cancer, and examining all candidate genes to identify genetic variations (polymorphisms) and their presence in multiple populations. Ultimately, this information will provide important insights about how the more common, sporadic (non-hereditary) cases of prostate cancer develop.

NCI's Cancer Genetics Network (CGN) is a vital scientific resource that supports collaborative studies on the genetic bases of cancer susceptibility as well as studies exploring mechanisms for integrating this new knowledge into medical practice, and addressing associated psychosocial, ethical, legal, and public health issues.

PROSTATE CANCER SCREENING

Current prostate cancer screening and early detection methods pose serious dilemmas for men and their health care providers. Many more prostate cancers exist in men over age 50 than ever become clinically apparent or significant. Although we believe that early detection, primarily through PSA screening, has decreased prostate cancer mortality, thus far we are limited in our ability to differentiate between tumors that will lead to fatal disease and those that will remain clinically insignificant. Recent research is providing important information that is expanding our understanding of prostate cancer biology, a prerequisite to developing diagnostic tools and identifying new targets for prevention, early diagnosis, and treatment. In addition, new technologies such as micro-arrays and proteomics are providing improved means of identifying diagnostic markers. The challenge will be to select the most promising markers and to determine how to validate and develop them into clinical diagnostic tests. The Early Detection Research Network (EDRN) was established to identify and validate markers for early detection and is developing the extensive tissue resources needed for these studies. In addition, the eight prostate cancer SPOREs are working to develop new diagnostic approaches and to deal with the complexities of validation studies. Validation studies require extensive tissue resources with associated clinical and outcome information.

PROSTATE CANCER PREVENTION

NCI is also supporting research on the prevention of prostate cancer, including studying the effect of diet on prostate cancer. Last summer NCI and a network of researchers known as the Southwest Oncology Group (SWOG) launched the Selenium

and Vitamin E Cancer Prevention Trial, or SELECT, to determine if these two dietary supplements can protect against prostate cancer, the most common form of cancer, after skin cancer, in men. NCI is receiving some supplemental support from the National Center for Complementary and Alternative Medicine for this trial. The study will include a total of 32,400 healthy men age 55 and older. More than 400 sites in the United States, Puerto Rico, and Canada are recruiting participants for SELECT, which will take up to 12 years to complete. SELECT is the first study designed to look specifically at the effects of vitamin E and selenium, both separately and together, in preventing prostate cancer.

PROSTATE CANCER TREATMENT

Although genuine options are available for curing prostate cancer when it is localized, we do not have reliable ways to predict the behavior of an individual cancer, nor do we know how to predict whether an individual cancer will respond well to one particular treatment compared to another. Moreover, while treatments for localized prostate cancer usually are effective, they are not *always* effective, nor are they free from troublesome side effects. We need to develop optimal treatments for both localized and systemic prostate cancer. NCI will focus on four major areas: (1) identifying markers of risk and response, (2) identifying endpoints for clinical trials, (3) developing new therapeutic agents, and (4) identifying optimal treatments for various stages of disease.

NCI is to providing support for these research areas through its SPOREs and RAID (Rapid Access to Intervention Development) Program. The SPOREs are focusing on aspects of prostate cancer biology that may be particularly useful in developing new treatments, as well as on how treatment effectiveness can be improved by gathering information about prostate cancer biology. The RAID Program expedites new agent development by making NCI's preclinical drug development resources and expertise available to investigators in universities and small to medium size biotechnology companies. Investigators selected for support are assisted with development steps necessary to enable Investigational New Drug (IND) application filing with the FDA and to begin initiation of proof-of-principle clinical trials.

In its quest to rapidly advance prostate cancer research, NCI is committed to developing more accurate models of prostate cancer. Prostate cancer researchers will use these models to screen drug candidates, conduct preclinical studies of new drugs, and better understand the biology of human prostate cancer. Currently, multiple models are available to the scientific community such as xenograft, cell lines, transgenic, reconstitution, spontaneous tumor, and hormonally induced models. However, limitations within each of these model systems have prompted NCI to support the development of additional models that more faithfully imitate the human disease.

NCI has established the Mouse Models of Human Cancers Consortium (MMHCC) and charged its members to use the latest techniques to develop and validate mouse models of human cancer. Prostate cancer experts from this consortium have established the Prostate Cancer Models Forum, which will focus on the development of mouse models for human prostate cancer.

DRUG DISCOVERY

Mr. Jackson: Dr. Andrew von Eschenbach, NCI director, has told the public that he envisions cancer treatment moving from a general chemotherapy "search and destroy" mode to one involving targeted and less toxic treatments, like Gleevec, for some forms of leukemia. The 1999 plan called for the establishment of at least 25 molecular target-based drug discovery initiatives for prostate cancer over five years.

Are we on target? What is the status of discovery?

Dr. von Eschenbach: In the NCI five year prostate cancer research plan from 1999, our vision was to develop three to five new prostate relevant therapeutic agents in1999, and a total of fifteen over the five year period. The Rapid Access to Intervention Developement (RAID) program of the NCI is designed to facilitate the translation of novel, scientifically meritorious cancer therapeutics from the lab to the clinic. Projects originate in the academic community, with applications accepted twice per year and evaluated by peer review. Successful investigators are granted access to NCI contract drug development resources. Since its inception in August 1998, the RAID program has committed to assist 62 preclinical development projects. Of these, four projects specifically target the treatment of prostate cancer, including:

a. A Novel Gene Therapy Approach for the Treatment of Prostate Cancer: a Preclinical to Clinical Transition (Dr. Svend Freytag, Henry Ford Health System);
b. Tumor-Specific Targeting of WTP53 By Anti-Transferrin Receptor Single Chain Antibody: New Therapeutic Strategy for Prostate Cancer Treatment (Dr. Esther H. Chang, Georgetown University Medical Center);
c. Enzymatic Activation of a Thapsigargin Prodrug by Prostate Specific Antigen (PSA) as Treatment for Metastatic Prostate Cancer (Dr. John Isaacs, Johns Hopkins University);
d. A Prolactin Growth Antagonist as a Potential Therapeutic for Androgen-Independent Prostate Cancer (Dr. Ameae M. Walker, University of California).

Dr. Freytag's agent entered human clinical trials in early-2001. The remaining prostate-related projects require further development efforts before they will be suitable for testing in humans. Additionally, several RAID projects provide nonspecific treatment of solid tumors and may also prove beneficial against prostate cancer, including:

a. Preclinical Development of PT523, a Potent Nonpolyglutamatable Antifolate (Dr. Andre Rosowsky, Dana Farber Cancer Center);
b. The Development of a Liposomal Formulation of Highly Lipophilic 7-t-butyldimethylsilyl-10-hydroxycamptothecin (DB67) (Dr. Thomas Burke, University of Kentucky, Markey Cancer Center);
c. Development of Novel Acting Inhibitor-DNA Methyltransferase (Dr. Norbert O. Reich; University of California at Santa Barbara);
d. Synthesis, Formulation, IND-Directed Toxicology of Intravenous Fenretinide & Safingol (Dr. C. Patrick Reynolds; University of Southern California, School of Medicine);
e. Testing of 12, 13-Desoxyepothilone B in Large Animals and Preparation of GMP Grade Materials for Phase I Clinical Trials (Dr. S. J. Danishefsky, Memorial Sloan-Kettering Cancer Center).

Dr. Rosowsky, Dr. Reynolds and Dr. Burke's projects will all enter human clinical trials in 2002. Dr. Danishefsky's project entered clinical trials in late-2001. Dr. Reich's project requires further development before it is suitable for testing in humans.

In addition, since 1983 the NCI has supported the National Cooperative Drug Discovery Group (NCDDG) Program which encourages multi-disciplinary teams of scientists to develop new agents and treatment strategies based on sound scientific rationales. One such group headed by Ronald Levy, Stanford University Medical Center, has concentrated on the development of new vaccines for the treatment of prostate and other cancers. A Phase III multi-centered trial including 240 patients with early metastatic prostate cancer is now underway. The vaccine was developed on the NCDDG with Reiner Laus at the Dendrion Corporation and consists of a fusion protein with prostatic acid phosphatase (PAP) and a growth factor, GM-CSF, which is loaded into a type of immune cell called dendritic cells that have been taken from an individual patient, loaded with the vaccine, and infused back into the same patient.

In fiscal year 2000, the NCI initiated a new program called the Molecular Target Drug Discovery (MTDD) Program to promote research on several cancers, including prostate. In contrast to previous eras where new agents were developed based on their ability to kill cancer cells, the new emphasis is on identifying control points in cancer cells. As part of the MTDD Program investigators are searching for vulnerabilities in cancer cells which can be targeted with new therapies. These vulnerabilities often can be found in signaling pathways important in causing and/or maintaining the cancer process. The new program also takes advantage of recent technological innovations which are speeding up the drug discovery process and making it more efficient. For example, recent advances in chemistry allow the production of thousands of compounds using combinatorial techniques to promote lead discovery and optimization. Robotics and miniaturization have fostered the development of high throughput screening techniques which increase the pace of identifying promising lead compounds.

A competition was held in FY 2000 which resulted in 40 awards for a total outlay of about $7.8 million in fiscal year 2001. Awards used different grant mechanisms: 21 two-year, exploratory grants; 11 cooperative agreement awards for more advanced projects; two supplements to existing grants to validate targets for their potential as drug discovery targets; and six grants to small businesses to develop their creative ideas into useful products for the marketplace. A second competition involving exploratory grants and supplements is ongoing with awards expected by the end of fiscal year 2002. We plan to fund about 29 exploratory grants and three supplements. Any one of these grants could identify and validate a target as well as develop an assay for a target that may be important for the treatment of cancer. At this time, our knowledge of exploitable targets for prostate cancer is still developing.

On March 14-15, 2002 NCI sponsored a workshop for the 11 NCI cooperative agreement awardees. At this first meeting, the investigators presented their studies which support basic research as well as translational research that will turn new information about cancer relevant targets and ligands for those targets into selective therapeutics that avoid the toxic effects of the "search and destroy"era drugs. Several groups presented findings that may have application to prostate cancer. For example,

NCI funded researchers at the University of California at San Diego are exploring heparan sulfate biosynthesis for possible drug targets. This pathway produces heparan sulfate proteoglycans on the surface of many cells. These products serve as co-receptors for several signaling pathways, including a variety of secreted growth and angiogenic factors on which tumor growth depends. Scientists are using genetic strategies to block the expression of various steps in the pathway to identify points of vulnerability. Once a validated target is identified, screening technologies are in place to identify compounds from natural product or synthetic libraries that block validated targets.

Researchers at the Fred Hutchinson Cancer Research Center have found that Bcl-2-related proteins confer cellular resistance to a wide range of drugs that induce cell death through apoptosis. They have found that myeloma cells are especially dependent on Bcl-xL for survival, but perhaps this, or a related protein, is also important in prostate cancer. The group has identified derivatives of antimycin A as particularly effective in binding to Bcl-xL and inhibiting the molecular pore function of Bcl-xL in the mitochondria. Drug design studies are in progress to identify more effective agents that block Bcl-xL, which should lead to selective apoptosis of myeloma and perhaps other types of cancer cells.

Purdue University scientists have identified a tyrosine kinase called EphA2 that is elevated 50 to 500 fold in a variety of malignant carcinomas, particularly cancer cells with metastatic potential, such as advanced prostate cancer. To validate this target, scientists are developing a series of antibodies that block the

action of this kinase. If successful, this approach could provide a powerful new way to block metastatic cancer spread in a number of cancer types that depend on this abnormality.

Researchers at the University of Texas MD Anderson Cancer Center are exploring key pathways important in angiogenesis for targets. Integrins that bind to vitronectin are highly expressed in neovasculature and play an important regulatory role in angiogenesis. This project is attempting to define the molecules involved in the alpha v beta3 and alpha v beta5-angiogenic signaling pathways. The research group has developed phage display peptide libraries and is currently panning (screening) these peptides for useful inhibitors to better delineate the pathways. Once a critical target is identified, antibodies or small molecule drugs can be developed that target appropriate signaling molecules that might control prostate and other clinical cancers.

Scientists at Memorial Sloan-Kettering Institute for Cancer Research are evaluating the hsp90 family of proteins as potential drug targets. These proteins, called chaperone proteins, play key roles in protein refolding, processing and conformational maturation of several key signaling proteins. Hsp90 proteins are overexpressed in many tumors including prostate and may play a role in maintaining the transformed phenotype. The goal of this project is to identify inhibitors of hsp90 family members using structural design and screening techniques. A lead compound, geldanamycin, has been identified but more selective compounds are being sought.

NCI intramural researchers at the Frederick Cancer Research and Development Center are studying ways to reactivate apoptotic or so-called death pathways that would efficiently and selectively kill cancer cells. Cancer cells have devised various ways to elude apoptosis, such as by losing the ability to release cytochrome c from mitochondria, a key event in the induction of apoptosis. The p53 tumor suppressor gene is lost or mutated in many types of cancer, including some cases of prostate cancer. Scientists will use screening techniques to search for inhibitors of regulators of p53 in tumors that retain p53 and will search for agents that affect downstream signaling events in tumors that have mutated p53. Thus, cancer cells which are surviving because of genetic defects in their p53 pathways should respond to death signals once agents are identified to reactivate the appropriate pathways. This is important because p53 abnormality had been associated with advanced metastasis and lethal hormonal refractory forms of prostate cancer.

NCI CENTER TO REDUCE CANCER HEALTH DISPARITIES

Mr. Jackson: When Dr. von Eschenbach headed the Integration Panel for the Department of Defense peer review prostate cancer research program, he recognized the need to accelerate research and training at institutions serving minority populations. The

DOD prostate cancer program has designed interesting initiatives that would create partnerships for historically black colleges and universities in order to enhance the research capital within institutions serving the black community.

During the past two years, I have regularly noted the slow pace at which the NCI Center to Reduce Health Disparities has undertaken new initiatives.

What specifically are NCI's plans to reduce the burden of prostate cancer on the black community? Will NCI support increased training and research initiatives for minority researchers and historically black colleges and universities?

Dr. von Eschenbach: The Center was created in December 2000 with Dr. Harold P. Freeman as its founding Director. We are rapidly moving forward with recruitment of a Deputy Director and Branch Chiefs for the Center. The Center acts as the cornerstone of NCI's efforts to address the unequal burden of cancer in our society. As the organizational locus for these efforts, the Center directs the implementation of and supports initiatives that advance our understanding of the causes of health disparities, and that develop and integrate effective interventions to eliminate these disparities. In this first full year of operation the Center has initiated a number of activities, and is promptly moving to incorporate all the NCI divisions and offices to participate in this challenge to support fundamental, surveillance and intervention research, training, and research dissemination and diffusion to eliminate the unequal burden of cancer in communities across the country.

Some of these activities include:

1. Launching a health disparities lecture series. The inaugural lecture in this series will be held on April 11th at NIH. Dr. Thomas Holt, the James Westfall Thompson Professor of American and African History at the University of Chicago will be speaking on "The Problem of Race in the 21st Century after 9/11."

2. Expanding support for NCI's Special Populations Network (SPN). The purpose of the SPN is to build relationships between large research institutions and community-based programs and to find ways of addressing important questions about the burden of cancer in minority communities.

3. Conducting the *Cancer Health Disparities Summit* (scheduled for July 15-17, 2002) to make the structure and function of the National Cancer Institute and the mechanisms by which it supports cancer research more transparent to grantees and others outside of the Institute. Its purpose is to teach the principles and practice of cancer control in a way that directly benefits the SPNs.

4. Supporting two rounds of extramural review to award up to $2.05 million in one-year supplemental grants to SPN investigators whose proposals are new and innovative and that address health disparities issues in their regions/communities.

5. Expanding the Center's research grant portfolio to include awards across relevant disciplines to examine gaps in knowledge and address questions that emerge from Center-supported "think tanks." These "think tanks" are comprised of professionals who have the background and experience in a variety of disciplines and who can provide the expertise, insights, and guidance the Center needs to shed light on the complex set of issues related to cancer health disparities and to identify gaps in current knowledge and recommend areas where further research is needed and interventions required. The Center has held two of these "think tanks" and is making final plans for subsequent meetings on these topics in May 2002 to identify NCI's next steps in addressing these major disparity issues:

    a. "The Effects of Racialism on Cancer Care Delivery" - Continues to examine issues emerging from a growing number of peer-reviewed studies published in leading medical journals showing that black patients, when compared with white patients of similar socio-economic status, insurance coverage, health status, and diagnosis, tend not to receive the same treatments as white patients. A limited number of studies have also shown that other race and ethnic minorities experience similar outcomes. The conclusions drawn from these studies has prompted CRCHD, in its first year, to identify this issue as a major focus of analysis in the Center's health policy research agenda.

    b. "Reducing Health Disparities in Geographic Regions of High Cervical Cancer Mortality" - The issue of cervical cancer mortality in rural populations was chosen as the first review for several reasons: there exists a long-standing (50 years) disparity in cervical cancer that makes it a critical issue to address; there are stable regional patterns of cervical cancer mortality disparities; and early detection, diagnosis and treatment of cervical cancer can be effective.

    c. "Promoting expansion of the Minority Institution/Cancer Center Partnership Program (MI/CCP)" - The NCI MICCP was initiated two years ago and will support four comprehensive partnerships by the end of FY 2002 to Johns Hopkins/Howard University, Vanderbilt/Meharry Medical College, University of North Carolina/North Carolina Central University, and M.D. Anderson/U. of Puerto Rico and one planning grant for a

comprehensive partnership to U. Alabama/Tuskegee/Morehouse School of Medicine. These partnerships are designed to increase the research being conducted at minority institutions, train more minority scientists and expand the research at NCI cancer centers focused on minority health disparities. This program has great potential and will be expanded.

NCI has a variety of initiatives and programs underway and planned for the future that will aid in the reduction of the burden of prostate cancer on the black community.

SOUTHERN COMMUNITY COHORT STUDY

NCI recently awarded a multi-million dollar grant to help determine why African Americans are more likely to develop cancer and die from the disease. The Southern Community Cohort Study is a long-term prospective cohort study of 90,000 African American and 45,000 non African American residents of the southeastern U.S. The current body of cancer etiology and prevention knowledge draws substantially from prospective epidemiologic studies, in which African Americans have been greatly under represented. Yet, African-Americans experience disproportionately high incidence and/or mortality rates for many major cancers and other chronic diseases for reasons that remain unknown. This cohort was designed to be large enough to begin analyses of specific risk factors for common cancers (prostate, lung, breast, colorectal) within the five-year study period. In addition, the large study size will enable the assessment of less common cancers that afflict blacks more than other racial groups. The biospecimen repository will provide an invaluable resource for evaluating biomarkers of cancer risk. The study should help answer questions regarding the etiology of prostate cancer and elucidate causes of the disparities in prostate cancer incidence and mortality across racial groups. The initiative is a collaborative effort of the Vanderbilt Ingram Cancer Center (Nashville, Tenn.), Meharry Medical College (Nashville, Tenn.), and the International Epidemiology Institute (Rockville, Md.).

MINORITY-BASED COMMUNITY CLINICAL ONCOLOGY PROGRAM

This programs, initiated in 1990, provides minority cancer patients, including those diagnosed with prostate cancer, with access to state-of-the-art cancer treatment and prevention and control technology. The Community Clinical Oncology Program (CCOP) provides support for expanding clinical research efforts in the community setting. Of the sixty CCOPs located in the U. S. and Puerto Rico, ten are Minority-based CCOPs. The Minority-based Community Clinical Oncology Programs (MBCCOPs) bring the advantages of state-of-the-art cancer treatment and prevention and control research to minority individuals in their own communities; increase the involvement of primary health care providers and other specialists with the MBCCOP investigators, providing an opportunity for education and exchange of information; and provide an operational base for extending cancer control and reducing cancer incidence,

morbidity, and mortality in minority populations by accelerating the transfer of newly developed technology to widespread community application. Applicants for the MBCCOP must document that at least 40 percent of their newly diagnosed cancer patients are from minority populations. There are over 110 minority investigators among the MBCCOPs.

SPORES

As I mentioned in a previous question, each of the eight prostate SPOREs is in the discovery phase of new potential biomarkers using cDNA and tissue microarray technologies. Through collaborative efforts the prostate SPOREs have developed in the past year the necessary infrastructures to validate relevant biomarkers for prostate cancer using high throughput analysis and technologies that will ultimately bring into clinical practice new biomarkers for diagnosis, prognosis, and treatment.

In addition, the prostate SPOREs as networks, are designing tissue microarrays to address studies on special populations including African-Americans, Hispanics, and Asian Americans. These multiethnic tissue microarrays will be used to test relevant biomarkers and compared with those found in the population at large.

One upcoming study on biomarkers will be investigating the caveolin-1 (cav-1) protein. This protein is specifically expressed in prostate cancer cells that have metastatic potential and are relatively androgen insensitive. Immunohistochemical analysis of prostatectomy specimens from lymph node negative patients demonstrated that cav-1 is an independent predictor of recurrence. Cav-1 protein levels are higher in prostate cancer specimens from African-American men than in specimens from White-American men. Human prostate cancer cells secrete cav-1 which promotes survival of human prostate cancer cells that do not express cav-1. Cav-1 can be detected in the serum of men with prostate cancer and preliminary data indicates that it may have diagnostic and prognostic significance. Further trials are needed to corroborate these findings.

INTERNATIONAL STUDY ON AFRICAN-CAUCASIAN DIFFERENCES

NCI is planning a coordinated, international, population-based, interdisciplinary case-control study of prostate cancer in Africa, and among African Americans and Caucasians in the U.S. This major effort will focus on elucidating the origins of prostate cancer. Special attention will be given to identifying the genetic and environmental determinants of the marked racial/international differences in the risk of clinically significant disease and the changing patterns among migrant populations. For each population group in the U.S. and Africa, the study will include a standardized and coordinated assessment of histologic and molecular characteristics of minimal and clinically significant disease; lifestyle and other environmental risk factors, based on

questionnaire and biospecimen assays; and susceptibility mechanisms, including genetic and hormonal factors. A pilot study is now underway in Ghana to evaluate the data quality and feasibility of conducting a well-designed case-control study with specimen collections in the African study population.

SELECT

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a large prostate cancer prevention study launched by NCI and a network of researchers known as the Southwest Oncology Group (SWOG). The study will determine if two dietary supplements, selenium and vitamin E, can protect against prostate cancer. Researchers are making a special effort to ensure a high rate of participation among African-Americans.

THE PROSTATE CANCER PREVENTION TRIAL

The Prostate Cancer Prevention Trial (PCPT) is a large, placebo-controlled, phase III study to test the drug finasteride for the prevention of prostate cancer in men ages 55 and older. Men with a family history of prostate cancer were aggressively recruited because they may have the greatest risk of developing prostate cancer.

PROSTATE CANCER RISK IN U.S. BLACKS AND WHITES

This project is a large, case-control study of prostate cancer among U.S. African Americans and whites in selected areas of Georgia, Michigan, and New Jersey. The study will attempt to identify risk factors for the disease and to explain the black/white differential in prostate cancer rates.

AFRICAN-AMERICAN HEREDITARY PROSTATE CANCER STUDY NETWORK

NCI has contributed seed funding to a collaborative study between the National Center for Minority Health and Health Disparities and the National Human Genome Research Institute (NHGRI). This study is an innovative research collaboration between investigators from Howard University and scientists in the NHGRI intramural research program. That collaboration has led to the founding of the National Human Genome Center at Howard University, focused on diseases that disproportionately affect individuals of African ancestry. Among the projects is the African American Hereditary Prostate Cancer (AAHPC) Study Network.

The initial aim of this study is to enroll 100 African-American families with prostate cancer in which at least four men, diagnosed at or before 65 years of age, are affected in each family and there are four other (unaffected) relatives available for study. African-American prostate cancer families of this description are almost completely missing from other pedigree collections, despite the higher incidence and higher lethality of prostate cancer in black men. Through a competitive review, the AAHPC

study network funded seven centers (Detroit, Chicago, New York, Atlanta, Houston, Columbia, and Washington, DC). For most of these, the Principal Investigator is an African-American urologist. Community acceptance and participation has been good. Blood samples and clinical data are sent from recruitment sites around the country to the Coordinating Center at Howard for DNA extraction and databasing. Over 76 families have already been identified and samples collected. DNA from these families is currently being intensively studied at NHGRI to see if linkage can be found to a known hereditary prostate cancer location on chromosome 1 as well as whether other linkages exist.

COMMUNICATION ABOUT PROSTATE CANCER

In 2001, the NCI's Cancer Information Service (CIS) (1-800-4-CANCER) responded to nearly 30,000 telephone inquiries about prostate cancer and distributed nearly almost 900,000 prostate cancer brochures and booklets , directly to patients and professional organizations as well as through collaborations with survivor groups (including a nation-wide program with US-TOO); and through churches, clinics and other community resources.

For example, a man with prostate cancer faces numerous decisions, and the sheer volume of relevant information can be overwhelming. Two NCI-funded Small Business Innovative Research (SBIR) grants have produced much-needed decision aids for men with prostate cancer. *Take Charge: For Men Newly Diagnosed With Prostate Cancer* is especially designed for African-American men, a group that is affected disproportionately by prostate cancer. Hosted by General Colin Powell, the broadcast-quality videotape has aired several times during prime time, and is available for use in hospital waiting rooms and clinic settings. Nominated for an Emmy and endorsed by the American Cancer Society, the film has also received the following:

- Finalist, 1999 Freddie Awards;
- Silver Award, WorldFest Houston;
- Bronze Award, National Health Information Awards;
- 2001 Tibbetts Award

The producer expects to promote the program via multiple channels over the next few years.

Communication will be integral to translating prostate-cancer research results into application and practice. NCI's communication professionals support our presence at professional meetings, in announcing advances through the media, in drawing researchers to information about research opportunities on our Web site, and in advising and supporting basic scientists as they make their advances available for more targeted applications. As scientific advances reach the clinical trials stage, the CIS helps men find information on prostate cancer prevention and treatment trials. By 2008, we can anticipate 1-800-4-CANCER to be answering substantially more prostate cancer inquiries, and NCI's Web site will be delivering prostate information to many more

visitors, consistent with anticipated changes in diagnosis, incidence, and demographics. Likely increases in the distribution of informational materials by 2008 will reflect significant increases in the number of local outlets, including churches, but may be proportionately reduced as we distribute a greater proportion of information electronically, a preferred option for many men. As more low-income people gain access to the Internet via technology centers in their communities, outreach to poor and minority families will grow. NCI is speeding this process through targeted programs of outreach to technology centers in several states.

The NCI is currently in its second year of funding partnerships between Minority Serving Institutions (MSIs) and NCI-designated Cancer Centers. This initiative already has funded five comprehensive partnerships designed to enhance the research at MSIs, increase the research focused on health disparities in minority populations and increase the number of minorities involved in cancer research. Three of these partnerships are to Historically Black Colleges and Universities (HBCUs) and centers, and they all are developing research programs focused on prostate cancer in blacks. In addition, numerous other planning grants devoted to research collaborations and training have been funded. This program reaches out to more than 400 MSIs and has been well received by both the MSIs and NCI-designated Cancer Centers.

In addition to the above initiatives, the NCI has expanded the number of Prostate Cancer Specialized Programs of Research Excellence (SPOREs) from 3 to 8 in the last two years. SPOREs, which are dedicated to bench to bedside research or translational research, devote considerable resources to the disproportionate incidence of prostate cancer in blacks and have career development programs that are required to recruit minorities scientists.

SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE

Mr. Jackson: The prostate cancer Specialized Programs of Research Excellence (SPORE programs) have created multidisciplinary teams at various centers to accelerate the movement of discoveries and observations back and forth among laboratory, clinic, and population settings.

In 1999, the plan called for the funding of nine or ten prostate cancer SPORE programs by FY 2003. Currently there are eight, and I commend NCI for moving forward on their commitment in this regard. However, I have recently heard that the future of some or all of these programs is in jeopardy this year because budgeted funds were moved into other NCI initiatives. If this is the case, it is very disturbing, and I would welcome your comments on the current status of the prostate cancer SPORE program.

Is it still NCI's intention to establish at least nine or ten programs and, if so, will NCI hit its target in FY 2003? In its 1999 plan, NCI suggested augmentation of the SPORE program to increase emphasis on prostate cancer etiology in African American

men. To what extent are the existing prostate cancer SPORE programs at Johns Hopkins, Memorial Sloan Kettering, Mayo, University of California at San Francisco, Baylor, Michigan, Northwestern and M. D. Anderson addressing the problem of prostate cancer in African American families?

Dr. von Eschenbach: In 2000 the NCI started an expansion of the SPORE program that will include additional organ sites and will expand existing organ sites. In particular for the prostate SPORE program, multiple receipt dates were created to increase the number of opportunities for applicants. This resulted in several applications received and funded during 2000-2002 years. The NCI is hoping to augment the number of prostate SPOREs to eleven in 2002 and to twelve in FY 2003 if funds are available.

A critical goal in prostate cancer research is to identify epidemiological, clinical and molecular markers related to prostate cancer progression. In addition to the research on biomarkers and tissue mocroarrays discussed earlier, a study has been proposed to follow-up on 1200 prostate cancer patients of all ethnicities seen at M. D. Anderson Cancer Center between 1990 and 2000. These men are participants in ongoing epidemiological studies for whom baseline clinical and epidemiological information has been collected and for whom banked specimens (DNA and tissue) are available. The objective is to identify clinical, lifestyle, and genetic factors that may play a role in disease progression. The first aim is to evaluate baseline epidemiologic (smoking, family history of prostate cancer), clinical (stage, Gleason score, tumor volume) and treatment parameters and their impact on prostate cancer progression. Information will be collected on health status through telephone interviews. Recurrence, biochemical failure, and death will be verified through medical records and death certificates. A second aim will be to evaluate genetic susceptibility by genotyping patients for polymorphic genes related to hormone metabolism: androgen receptor, 5-a-reductase type II, CYP17, CYP3A4, 3-b-hydroxysteroid dehydrogenase type II, and vitamin D receptor. The study will also result in the creation of tissue microarrays to allow the analysis of gene expression by *in situ* hybridization for a panel of tumor progression markers (e.g., MMP-2, MMP-9, VEGF, and E-cadherin) in a subset of 375 cases of different ethnicity (200 whites, 100 African Americans, and 75 Hispanics). Finally, these molecular, epidemiologic and clinical data will be integrated to investigate how the interplay between these characteristics modifies prostate cancer progression. Findings from this project could be useful in identifying patients at high risk of prostate cancer progression and could assist clinicians in determining the most appropriate treatment strategy.

At the Baylor University SPORE, an upcoming study on biomarkers will be studying the caveolin-1 (cav-1) protein. This protein is specifically expressed in prostate cancer cells that have metastatic potential and are relatively androgen insensitive. Immunohistochemical analysis of prostatectomy specimens from lymph node negative patients demonstrated that cav-1 is an independent predictor of recurrence. Cav-1 protein levels are higher in prostate cancer specimens from African-

American men than in specimens from White-American men. Human prostate cancer cells secrete cav-1 which promotes survival of human prostate cancer cells that do not express cav-1. Cav-1 can be detected in the serum of men with prostate cancer and preliminary data indicates that it may have diagnostic and prognostic significance. Further trials are needed to corroborate these findings.

In addition, at the Johns Hopkins Prostate Cancer SPORE, the major effort at ascertaining prostate cancer etiology in African-Americans has involved genetic and family studies of prostate cancer susceptibility genes. A formal collaboration with the Howard University Cancer Center, as well as funds from the Prostate Cancer SPORE and from an NCI Howard-Hopkins Partnership Grant, has targeted African-Americans at risk for prostate cancer for genotyping analyses. Each investigator is an accomplished prostate cancer geneticist. By combining families and populations at Johns Hopkins and at Howard, differences in prostate cancer etiology and risk between African-Americans and Caucasians can be evaluated.

DATA SHARING

A focus of our research is to develop a national informatics network to facilitate the sharing of resources across research initiatives and programs. In the next few years, tissue-based and bioinformatics systems for prostate cancer research will expand greatly; however, prostate cancer research currently is hampered by an inadequate infrastructure for tissue acquisition, storage, and use; data sharing across disciplines; and information sharing to link the efforts of various initiatives and programs. For example, the limited tissue repositories available are not closely linked with appropriate clinical, pathology, and epidemiologic information. There are too few databases containing this information to serve the burgeoning needs of basic, clinical, and epidemiologic researchers. These materials and supporting informatics need to be made widely available. Databases must be inter-linked among multiple programs and initiatives and must form part of a broader informatics network. The databases need to include genetic information to facilitate gene discovery, clinical data with all necessary information, a catalog of human prostate cancer, Expressed-Sequence Tags, family registries, and epidemiologic databases. Establishing the Cooperative Prostate Cancer Tissue Resource will meet some of the research community's need. The SPOREs, along with the Cancer Centers program are involved in this effort.

NCI is committed to developing more accurate models of prostate cancer. Prostate cancer researchers will use these models to screen drug candidates, conduct preclinical studies of new drugs, and better understand the biology of human prostate cancer. Currently, multiple models are available to the scientific community such as xenograft, cell lines, transgenic, reconstitution, spontaneous tumor, and hormonally induced models. However, limitations within each of these model systems have prompted NCI to support the development of additional models that more faithfully

imitate the human disease. NCI plans to fund supplements for grants to support development and validation of prostate cancer models in mice and other animals. Such support may be extended to Cancer Center Core grants and SPORES.

TRANSLATION OF RESEARCH ADVANCES INTO TREATMENT

Mr. Jackson: While we have witnessed tremendous advances in evidence-based treatments for schizophrenia, this knowledge has generally not been adequately translated into improved clinical care ~~in the real world~~. As was demonstrated in the landmark 1998 Schizophrenia PORT study, conducted and published jointly by the University of Maryland and Johns Hopkins University, this gap between science and accessible treatment has never been wider. Moreover, this lack of "translation" is at its worst in the African American community, leading to significant health disparities. The study showed that African Americans with schizophrenia were more likely to experience overmedication with anti-psychotic medications, increased side-effects, and under-treatment of depression to a higher degree than other racial/ethnic groups.

What is NIMH doing to improve the translation of scientific advances into real world treatment, in general, and especially in the African American community?

Dr. Nakamura: NIMH is both aware of and disturbed by the finding that African Americans with serious mental illness are more likely to be misdiagnosed as suffering from schizophrenia and consequently over-treated with anti-psychotic medication. The Institute has sponsored a number of studies that document the problems with diagnosis, access to care and quality of care received by the African-American community. In an effort to develop a targeted research program to examine diagnostic issues in racial and ethnicity groups, a *Culture and (Mis)Diagnosis Working Group* was convened in August 2000 and NIMH is currently funding research to evaluate possible causes of misdiagnosis in African Americans in order to develop strategies to eliminate this serious problem. (R01 MH 56352; P01 MH58565). Special activities have been funded in collaboration with the National Center on Minority Health and Health Disparities to ensure that underserved populations, including the African-American community, are included in these studies. In addition, all new treatment and prevention grants that NIMH funds are expected to include diverse community populations in their studies. A new research Centers program was launched this year that provides funds for researchers to interface with the community to develop treatment and preventive interventions that are relevant to their needs. These Centers will also study ways to improve the actual delivery of care in those communities. In addition, NIMH has awarded a large contract to Howard University to develop collaborative research efforts with the Institute's Intramural Research Program to ensure adequate representation of diverse populations in the clinical research conducted by NIMH staff investigators.

With respect to the translation of evidence-based treatments into improved clinical care for all Americans, NIMH has assigned priority to research designed to ascertain that treatments for mental illness are effective when applied to community

populations. Key to this initiative are five large clinical trials that are testing how well treatments work in the diverse populations typically encountered in a range of clinical care settings, including office-based practices and the primary care sector. NIMH also has created a new program in dissemination research to fund studies that seek to understand the best ways to ensure that quality services are provided to community populations, including African-Americans.

TUESDAY, MARCH 19, 2002.

FUNDAMENTAL RESEARCH: BIOMEDICAL RESEARCH IN THE FUTURE

WITNESSES

DR. RUTH L. KIRSCHSTEIN, M.D., ACTING DIRECTOR, NIH

DR. MARVIN CASSMAN, DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

DR. JAMES F. BATTEY, JR., DIRECTOR, NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

DR. RICHARD NAKAMURA, ACTING DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH

DR. GLEN R. HANSON, ACTING DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE

DR. JUDITH L. VAITUKAITIS, DIRECTOR, NATIONAL CENTER FOR RESEARCH RESOURCES

DR. ELLI EHRENFELD, DIRECTOR, CENTER FOR SCIENTIFIC REVIEW

KERRY WEEMS, ACTING DEPUTY ASSISTANT FOR BUDGET, DHHS

OPENING REMARKS

Mr. REGULA. Okay, we will get started. We have a lot of witnesses that are going to need some time.

Dr. Kirschstein, we're happy to welcome you back. You're getting to be a regular here. We're always happy to have you and your team. We'll let you introduce your team as they each speak, we'll try to do the whole panel. Maybe Mr. Obey and I may have a couple of interruptions, if we have questions. Otherwise we'll have questions when they're finished.

Dr. KIRSCHSTEIN. Mr. Chairman, Mr. Obey, we're pleased to be here for this panel, which will expand on what was discussed the other day. To allow biomedical research to make progress toward the prevention, diagnosis and cure of diseases that assuredly will continue to afflict mankind for years to come, we must acknowledge that considerable resources are needed.

These include modern day laboratories and equipment, especially expensive and large instruments, the latest information technology, repositories of chemicals, cells, tissues and genes, animal models of disease, as well as highly creative, highly motivated and well prepared researchers who have been trained to have the requisite up-to-date research skills to recognize important biomedical problems and the ways to solve them.

I discuss these issues in my written testimony which has been submitted for the record. The panel today will address these needs, which are limited to not just those of the institutes and centers they represent, but are required for future studies by the biomedical research enterprise in general.

INTRODUCTIONS

Today's panel members are Dr. Marvin Cassman, to my immediate left, the Director of the National Institute of General Medical Sciences, who will discuss research training of young scientists. Dr. James Battey, Director, National Institute of Deafness and Other Communications Disorders, who will expand on the career development programs for researchers, and also discuss animal model systems.

Dr. Richard Nakamura, to the far left, the Acting Director of the National Institute of Mental Health, whose topic is multidisciplinary neurosciences research. Dr. Glen Hanson, to my immediate right, the Acting Director of the National Institute on Drug Abuse, who will discuss clinical trials. Dr. Judith Vaitukaitis, to his right, the Director of the National Center for Research Resources, who will expand further on clinical trials and also discuss the need for research facilities and extramural construction as well as modern day laboratory equipment and instrumentation.

Finally, on my far right, Dr. Elli Ehrenfeld, the Director of the Center for Scientific Review, who will discuss the peer review system. We are joined by Mr. Kerry Weems from the Department.

In addition, I will provide information, if requested, on the infrastructure on the NIH campuses themselves, namely the buildings and facilities program and the intramural research training activities.

Dr. Cassman.

RESEARCH TRAINING

Dr. CASSMAN. Thank you, Dr. Kirschstein.

Good afternoon, Mr. Chairman, Mr. Obey. The mission of the National Institutes of Health is both to support research that will lead to an improvement in the Nation's health and to ensure that there is an adequate supply of trained researchers to aid in the pursuit of this goal. The two efforts are tightly linked in the United States by the fact that most of the basic research in this country is conducted in academic laboratories. As has been often noted, one of the great strengths of American science is that new discovery in the training of the next generation of discoverers takes place in the same locations.

Research training has been part of the NIH mission since its earliest days. Many, actually most of the current training programs derive from the National Research Service Act, which was established in 1974. In fiscal year 2001, the NIH research training budget for pre- and post-doctoral students equaled $576 million.

In addition, there is a still larger number of students and postdoctoral fellows that are supported through their employment on research grants. While contributing to the goals of the research program being supported, the students also complete an essential part of their apprenticeship in research. The training grant mechanism also allows NIH to target areas of emerging interest, such as biotechnology and bioinformatics. They also serve the purpose of addressing broader NIH goals such as bringing under-represented minorities into the research work force and providing training in scientific ethics.

Additionally, the NIH uses research career development awards for specialized training. These are targeted to investigators at the post-doctoral level and beyond. In recent years, NIH has used the RCDA to address the shortage of clinical investigators. There is also a specialized program called the Medical Scientist Training Program, the MSTP program, that generates students with dual degrees M.D.s and Ph.D.s. These people are very highly sought after; they tend to be on the frontier in translating basic biological research into clinical practice. Almost all the training programs are interdisciplinary in their function.

In summary, research training is a critical part of the NIH mission. In the words of a 1988 report from the Office of Technology Assessment, "Policy makers should seek to prepare a cadre of versatile scientists and engineers for research and teaching careers, invest in an educational system that creates a reservoir of flexible talent for the work force and ensure opportunities for the participation of all groups." This is precisely what the NIH training programs have attempted to do and have done, with considerable success. That's been attested to by many reports over the years, and in particular, some recent reports from the National Academy of Sciences and an internal NIH study that tracked career progression.

The training programs are not simply ancillary to our research efforts; they are integral to it and they operate together with the research programs in a highly coordinated fashion. Thank you. I will be happy to answer any questions you may have.

[The justification follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Statement of the Director, Dr. Ruth L. Kirschstein

to the House Appropriations Subcommittee on Labor-HHS-Education

March 19, 2002

on Fundamental Research: Biomedical Research in the Future

accompanied by:

Dr. Marvin Cassman, Director, National Institute of General Medical Sciences
Dr. James Battey, Director, National Institute on Deafness and Other Communication Disorders
Dr. Richard Nakamura, Acting Director, National Institute of Mental Health
Dr. Glen Hanson, Acting Director, National Institute on Drug Abuse
Dr. Judith Vaitukaitis, Director, National Center for Research Resources
Dr. Ellie Ehrenfeld, Director, Center for Scientific Review
Ms. Susan Quantius, Associate Director for Budget
Mr. Kerry Weems, Acting Deputy Assistant Secretary for Budget, DHHS

OPENING STATEMENT OF DR. RUTH L. KIRSCHSTEIN

FUNDAMENTAL RESEARCH: BIOMEDICAL RESEARCH IN THE FUTURE

MARCH 19, 2002

Mr. Chairman, Members of the Committee:

We are pleased to be here for this panel, which will expand on what was discussed yesterday. To allow biomedical research to make progress toward the prevention, diagnosis, treatment, and cure of diseases that assuredly will continue to afflict mankind for years to come, we must acknowledge that considerable resources are needed. These include modern day laboratories and equipment, especially expensive and large instruments; the latest information technology, repositories of chemicals, cells, tissues, and genes; animal models of disease; as well as highly creative, motivated and well-prepared researchers who have been trained to have the requisite up-to-date research skills to recognize important biomedical problems and new ways to solve them.

The panel today will address these needs, which are not limited to just those of the Institutes and Centers they represent, but are required for future studies by the biomedical research enterprise in general.

Below are examples of such essential requirements and ways to achieve their fulfillment.

PREPARATION OF NEW BIOMEDICAL RESEARCHERS

Continuing research that will combat disease and improve health requires capable, inspired, and motivated scientists for generations to come. The Institutes and centers support the training of scientists in areas relevant to their missions, as well as in areas of scientific opportunity such as biotechnology and bioinformatics and training to prepare researchers to meet the ethical issues encountered in performing research.

Career development awards are used for beginning clinical investigators to learn how to conduct research involving human subjects – a growing need given the increased emphasis on translating laboratory science to the clinic and the current shortage of medically-trained researchers.

MODEL SYSTEMS

Much of the progress in understanding and treating human disease has come from research using experimental animals, especially the mouse. Because mice and humans share virtually the same set of genes, the sequence of the mouse genome will greatly aid scientists trying to understand the structure of the human genome, as well as human development and diseases. The Mouse Sequencing Consortium, six NIH Institutes

along with four organizations from the private sector, is accelerating the work needed to sequence the mouse genome. The accelerated time frame will speed the discovery of genes important in normal and disordered organ function in the mouse and thus expedite an understanding of human health and disease.

CLINICAL TRIALS

Several NIH Institutes have organized nation-wide networks to hasten the process of moving basic findings from the laboratory into the health care system. For example, research supported by the National Institute on Drug Abuse (NIDA) has produced a broad array of pharmacological and behavioral treatments to combat drug abuse, but until NIDA established its National Drug Abuse Treatment Clinical Trials Network (CTN) in 1999, there was no systematic way to test and bring effective treatments into standard clinical practice for the more than 4 million people in this country in need of treatment for drug abuse.

The CTN has grown from its original 5 sites to now include 14 regional sites across the country. Each of these centers typically forms partnerships with 5 to 10 community treatment programs in their region, allowing treatments to be delivered by community health workers at the community level.

Similarly, the National Institute of Mental Health (NIMH) is expanding its Research units on Pediatric Psychopharmacology and Psychosocial Interventions, a network of major clinical centers that permit multi-site clinical trials so that interventions for children with mental illness can be determined to be safe and effective.

NEUROSCIENCES RESEARCH

At this moment in history, a unique opportunity exists for an unprecedented alliance of scientific disciplines and technologies focused on the brain to speed research on some of the most devastating diseases affecting humanity: schizophrenia, stroke, spinal cord injury, depression, drug and alcohol addiction, autism, Alzheimer's disease, Parkinson's disease, blindness, deafness, attention deficit hyperactivity disorder, chronic pain, and a wide array of cognitive problems.

To pursue this opportunity, NIH is in the process of constructing the Neuroscience Research Center (NRC) on the NIH campus. Seven Institutes are currently collaborating to build strong translational, cross-institute research on disorders of the human brain.

By fostering interaction among diverse disciplines, the NRC will increase the pace of discovery throughout neuroscience and will hasten the translation of new knowledge into clinical applications.

INSTRUMENTATION

Rapid progress in medical research is more and more dependent upon the availability of advanced instruments and other devices that often cost well in excess of half a million dollars each. The National Center for Research Resources (NCRR) has begun the High End Instrumentation (HEI) program, to assist institutions around the country in buying instrumentation for basic and clinical studies. Such instruments often cost more than $750,000. They include very high-field NMR spectrometers, extremely sophisticated imaging systems and electron microscopes, high-resolution mass spectrometers, and high-performance supercomputers.

Complementing this program is NCRR's shared instrumentation program, which provides instruments in the $100,000 to $500,000 range to be shared by scientists.

PEER REVIEW OF GRANT APPLICATIONS - CHALLENGES FOR THE CENTER FOR SCIENTIFIC REVIEW (CSR)

Peer review of investigator-initiated research has been the bedrock of the success of American science. The scientific landscape is rapidly changing as fundamental discoveries are applied to human health problems. CSR is reorganizing and creating new study sections to meet this challenge. Efficiency and effectiveness will improve with the electronic submission of grant applications and the ability to perform peer review on-line.

Today's panel members are:

Dr. Marvin Cassman, Director, National Institute of General Medical Sciences
Dr. James Battey, Director, National Institute on Deafness and Other Communication Disorders
Dr. Richard Nakamura, Acting Director, National Institute of Mental Health
Dr. Glen Hanson, Acting Director, National Institute on Drug Abuse
Dr. Judith Vaitukaitis, Director, National Center for Research Resources
Dr. Ellie Ehrenfeld, Director, Center for Scientific Review

In addition, I will provide information if requested about the infrastructure on the NIH campuses themselves, namely the Buildings and Facilities Program and the Intramural Training Activities.

CAREER DEVELOPMENT AND RESEARCH TRAINING

Dr. KIRSCHSTEIN. Dr. Battey.

Dr. BATTEY. Mr. Chairman, Mr. Obey, it's a pleasure to be here. I'd like to begin my remarks by thanking the NIGMS for supporting me in their MD-PhD program a little over 25 years ago. That was how I got my start in research. I'm grateful to this day for that support.

The NIDCD, and I believe all the NIH institutes, understands clearly that if we're going to spend the budgetary resources that we are so generously given each year in the best way possible, we need to continually replenish our cadre of investigators with bright, young, well trained scientists. The best and the brightest of American youth need to be attracted into the biomedical research endeavor, or we will not completely fulfill the potential that we have to realize—this enormous biomedical research opportunity that is before us.

Several years ago, the NIDCD convened a work group on career development and research training, where we brought in a number of our investigators and members of our scientific community to advise us on how we could do a better job of training and developing the careers of young investigators. We received a whole list of recommendations, many of which were directed towards, in particular, getting clinician scientists into the research arena.

If you like, I can go into the specifics of all of these. But suffice it to say that we have implemented all of those recommendations and we already have early indicators that we're getting better, brighter young people into the research endeavor. That's extremely satisfying.

We're also doing a better job of keeping clinician scientists in the research endeavor, rather than having them drift off into clinical practice, which has been one of the things that's often happened in the past.

TRANS-NIH INITIATIVES

So maybe I'll move along to speak just for a few minutes about animal models, as Ruth had promised I would. This topic really falls into the category of infrastructure. I'm going to talk about two trans-NIH initiatives, one of which was an initiative to accelerate the pace at which the mouse genome was sequenced. This initiative was guided by the leadership of Francis Collins, the Director of the National Human Genome Research Institute, and you might ask me why sequence the mouse genome.

The mouse is really unique among mammalian models. It is unique in the sense that we have very good control of the genetic background. What do I mean by that? What I mean is that within a given in-bred strain of mice, all members of that in-bred strain are basically genetically identical. There are no differences, which allows very clean consistent experiments to be done. Scientists are able to specifically manipulate the genome of the mouse, and to determine the consequences. It's a wonderful tool for allowing us to understand gene function.

Many of the organ systems in the mouse are very similar to that in the human. So what we learn about the fundamental biology

and diseases and disorders of those organ systems in the mouse can be readily translated into the human. Finally, maybe the most powerful argument for sequencing the mouse genome quickly is that there is no better tool than a similar but not identical mammalian genome for annotating the human genome.

What I mean by annotating is determining where the boundaries of the genes are and the numbers of the genes. By aligning the mouse and the human genome, one can find the beginnings and the ends of genes in the area of the human genome where we suspect there is a gene, but because this is the first time it's ever been seen, we don't know exactly where it begins and ends.

A second trans-NIH initiative involves a number of institutes interested in making the mouse a more powerful model system. The way that they are going about that is by funding centers. Within these centers, scientists are systematically creating random mutations throughout the genome of the mouse and then subjecting those mice to phenotypic studies. They look for elevated seizure threshold, they might look for a dumb mouse that has a hard time running the maze. They might look for a deaf mouse that can't hear, they might look for a blind mouse.

Then scientists can take these animal models and go back and find the mutation in the gene that causes the abnormality. Very often, it turns out that these are the same genes that underlie diseases and disorders in humans that are analogous to those that are found in the mouse. These are just two examples of infrastructure resources, both trans-NIH initiatives, both voluntary contributions on the part of the institutes. I think both initiatives will accelerate greatly the discovery of the genes involved in various diseases and disorders of human beings as well as contribute to a fundamental understanding of how those organ systems work.

REVOLUTION IN BRAIN SCIENCE

Dr. KIRSCHSTEIN. Dr. Nakamura.

Dr. NAKAMURA. Thank you.

When I was going to graduate school in the 1970s, we thought that genes were instructions for creating proteins that determined completely the structure of the brain. Not only that, we thought that that structure was fixed by the time you were about 20 years old, and from then on, it was only downhill, the only thing you could do is lose neurons.

Today, we have a vastly different picture of what's going on in the brain. We now know that our brains are actively constructed by an interaction between the genes and our experience and our environment. What we learn, in fact, affects the structure of the human brain. This poses as a problem for us something very different than what we thought early on.

Not only that, we had thought there were no new neurons growing in the brain after the age of, let's say, 20. But now we know that neural stem cells in the brain, these are natural stem cells in the brain, are constantly producing new neurons. These new neurons keep going, and we see new neurons in adults through the age of 77. That means through at least eight decades of life, we are constantly renewing our brains. These neurons are coming into place and helping us, among other things, remember things.

These discoveries were fundamental to understanding a revision of what's going on in the brain and we also know that things like stress reduce the number of new neurons and things like exercise increase the number of new neurons. That study was done in rodents, so I can't promise you that it happens to human beings. But after I heard this result, I went out and bought a treadmill. [Laughter.]

ADVANCES IN BRAIN IMAGING

Dr. NAKAMURA. So I wanted to show you, though, that in order to get these results, we needed to have a lot of new technology, new infrastructure, and we also needed to have scientists of all stripes working together. Here's just an example of what we knew 10 years ago and what we knew yesterday in two sets of results.

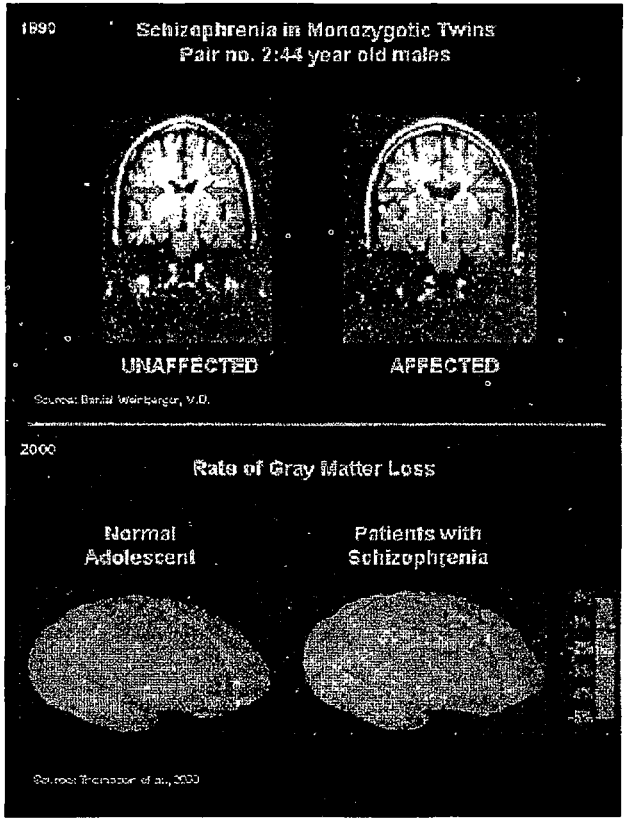
The top image is one that many of you have seen before, this picture from two twins with schizophrenia, one with the disease and one without. The one with bigger holes in the brain, bigger ventricles, is the one with schizophrenia. This was taken as an example of how schizophrenia is a real brain disease. But it was a pretty primitive example. The definition is weak, the change in ventricle size is something that occurred over a lifetime, and we couldn't really say that this was due to schizophrenia itself.

However, the pictures below show much more detail and they show pictures of the brain taken at two different points during development of those who are at risk for early onset schizophrenia. The individuals on the right are those patients who developed schizophrenia. It shows that those who develop schizophrenia lost a significant number of neurons. The red portion are those areas of the brain in which they lost neurons during development.

This shows for the first time that schizophrenia is an active process that definitely affects the brain. This required animal models, molecular biology, neuroimaging physicists, behavioral scientists, clinicians and basic scientists.

Thank you.

[The information follows:]


1990
Schizophrenia in Monozygotic Twins
Pair no. 2: 44 year old males
UNAFFECTED
AFFECTED
Source: Daniel Weinberger, M.D.
2000
Rate of Gray Matter Loss
Normal Adolescent
Patients with Schizophrenia

Dr. KIRSCHSTEIN. Dr. Hanson.

Dr. HANSON. Mr. Chairman and other members of the Subcommittee, it's a pleasure to be here and talk to you about how NIDA uses research and technology and infrastructure to work with the Nation to deal with the serious problems of substance abuse, including the problems of tobacco abuse. These are issues that cost this Nation approximately $300 billion a year as well as destroy countless numbers of families and individual lives.

We have been employing recent neuroscience technology to elucidate the underlying mechanisms of drug addiction. Just as an example, you can see on this chart the representation of two different brain systems. The system in red is the underlying system that seems to be responsible for initiation of substance use. It tends to be a system that's very reward driven.

After persistent or continuing use, drug administration becomes more compulsive and seems to be driven by the systems seen in purple. There's actually a shift in brain circuitry that's responsible for what we know to be a rewarding or initiating response and what occurs in addiction or a compulsive, more of a motoric system. This new perspective of shifting brain mechanisms allows us to develop more effective prevention and treatment approaches that will help people at various stages of the addiction process.

It's important that we have in place an infrastructure that will allow us to take these kinds of breakthrough discoveries and apply them in such a way that they will be practical and be able to be applied in clinical settings. NIDA's clinical trial network is such an infrastructure. It consists of 14 nodes and 90 community clinics spread across the country, as you can see in this graphic.

The pink asterisks are those nodes that are in place. The white ones are nodes that we anticipate or that we hope we will be able to bring into that system. Currently, this network is testing more than a dozen science based treatment protocols, and identifying how to adapt these therapeutic strategies for community use.

As I said, we're anticipating expanding the network, trying to go into under-served populations such as diverse minority groups and rural communities.

Finally, it's important for NIDA to take this information and these discoveries and facilitate their dissemination into general practice. I recently returned from a blending clinical practice and research conference in New York City where nearly 1,000 people from academia and treatment communities came together to discuss how new research findings could be applied. At this meeting, Dr. David Vlahov, a NIDA grantee, reported on the effects of stress on substance abuse after the 9/11 event. His data showed that there has been an increase in tobacco use, marijuana use and alcohol in much of Manhattan.

These kinds of results help NIDA to identify where it needs to place its emphasis as far as research is concerned and some recent discoveries looking at the mechanisms of stress have actually provided some ideas and some potential strategies to deal with stress in the clinical realm that will help us prevent and treat these kinds of drug abuse issues.

Because of your support, these are exciting, unprecedented times of opportunity. With your continued help, I'm sure that we and other members of NIH will be able to continue to make a difference in the health and the lives of the people of this country. Thank you.

INSTRUMENTATION

Dr. KIRSCHSTEIN. Dr. Vaitukaitis.

Dr. VAITUKAITIS. Mr. Regula, members of the Subcommittee, I am pleased to have this opportunity to discuss the key role instrumentation plays in modern research.

Research is changing. The paradigm is moving toward an integrative or systems approach, rather than a reductionist approach. Instead of studying things down to the molecular and atomic level, we study them in an intact cell or an intact system. It's akin to putting Humpty Dumpty back together again to study how the parts interact, as we measure them with a variety of instruments.

Why are we using this integrative or systems approach? Research questions have become much more complex. Consequently, they need a team of investigators, who range from experts in technology, like physicists, bioinformaticists, and bioengineers, to well-trained physician investigators and basic scientists. The makeup of the team will vary over time depending on the kinds of questions being asked.

The systems approach is heavily dependent on research instrumentation and on bioinformatics. It requires what we term high throughput. We gather a lot of technical information in a short period of time. We have to analyze it, which requires high end computation, and experts in developing programs that will actually allow investigators to visualize the data, to predict where they should go next and what experiments should be done next.

Equipment needed includes tools like cell sorters, confocal microscopes that cost several hundred thousand dollars. Investigators can apply to NIH for that type of equipment through the shared instrumentation grant program.

Recently, we became aware of a need for higher end equipment costing more than $750,000. Some items may actually cost up to several million dollars, for example, cryoelectron microscopes and NMRs.

We published a program announcement last fall for the high-end instrumentation program, and expected just a few dozen applications. We were wrong. We received considerably more, underscoring the need for this high-end equipment. I have approached my colleagues from other institutes and they have pledged to help pay for some of this high end equipment that's absolutely essential for modern day research.

SYNCHROTRONS

We have another way of providing access to instrumentation. We support a network of biomedical technology centers throughout the country, including centers that do crystallography using synchrotron radiation. It costs about $10 million to build a synchrotron beam line. These kinds of equipment need to be shared by many investigators through a centralized resource. We are able to do that

and support almost half of all the crystallographic beam lines that are available in this country.

We wanted to increase the throughput of crystal studies at these synchotrons. We asked one of the sites to develop a technique to do that, because it is cheaper to increase the throughput than build new beam lines. We thought that if they improved the technique by about 20 percent, it would help immensely. In short, they used robotics to place a crystal on the beam line and found a new way of making crystals. They not only met our 20 percent mark, they increased through put a thousand-fold. We think, in reality, bench testing will show something on the order of a 10 to 20 fold increase in throughput. This will greatly facilitate studies of macromolecules from the various genomes that are almost completed including human and many others.

VIRTUAL LABORATORIES

There is another way that one can access that instrumentation through what we call virtual laboratories. Separate investigators can work with someone else at a distance over the internet. For example, at the synchrotron I was describing, if someone wants to send their samples there to be uploaded by robot, they can control them with their own computer in their office.

We can create a virtual laboratory in a scientist's office. It contacts the Stanford synchrotron site, the robot is instructed to load the crystal. The researcher controls the synchrotron and gathers the desired data. It's then sent to the San Diego supercomputer center and comes back with coordinates and a mockup of what the macromolecule may look like.

Then, the researcher can use another program over the internet to define where a substance may bind to more than one place within that molecule. Using another data set, potential molecules that can fit into that binding site can be identified.

What I've described is basically a way of doing structure based design for new drugs. One can also use these tools for other purposes.

In summary, modern research is increasingly complex, and requires a multidisciplinary team, modern laboratories and a systems or integrative approach. Because this approach is very heavily data dependent, we need to provide access to teraflop computing, which we have begun to do through the internet, using a biomedical informatics research network that we are building with the National Science Foundation and several universities across the country.

Thank you.

PEER REVIEW PROCESS

Dr. KIRSCHSTEIN. Dr. Ehrenfeld.

Dr. EHRENFELD. Mr. Chairman, members of the Subcommittee. Several of my colleagues around the table have described new scientific findings, resource needs and training needs in the country. I listened to all that is happening in the biomedical research world with pride and pleasure.

I now want to focus on how we identify and select the research projects that NIH grantees are working on. So I will take just a

few minutes to briefly outline how the NIH peer review process works and describe some of our current challenges and solutions. Then of course will be happy to answer questions.

There are two levels to the peer review process at NIH. The first is the initial review, which is a review of grant applications for scientific and technical merit. It is conducted by panels of outside scientific experts predominantly from the research community. They come to what we call a study section meeting three times a year. The Center for Scientific Review conducts this initial review of about 70 to 75 percent of the applications submitted to NIH. Each institute or center conducts its own review of a subset of the remaining applications.

The second level of review is done by the funding institute itself, which by law has a national advisory council that is designed for that purpose. A council unlike a study section, includes a much broader spectrum of individuals. It certainly has scientists in the field, but it also has members of the interested lay community; representatives of advocacy groups, health care providers, ethicists; and a much broader spectrum of people. Council members weigh very heavily the scientific evaluations that are provided by the initial review groups. But they also consider the need to fund certain areas of research because of public health needs or because scientific opportunities have opened up in the field.

In the end, it is the institute that makes the funding decision based on both advice, from the initial review for the scientific merit and the second review for programmatic relevance to the science, the field, and the area that need to be supported.

Many will agree that the peer review system is the major determinant of the success of the biomedical research enterprise in the United States. And the study section itself is probably the most critical part of the peer review process. It is dependent upon two very critical elements.

The first is to have the right people sitting around the table making the evaluations. Having the right scientific expertise to evaluate applications is what allows the most promising and the most meritorious applications to be identified. Our staff in the Center for Scientific Review and in the institutes solicits reviewer nominations very broadly, then identifies and recruits appropriate reviewers with diverse scientific outlook, and ethnic, gender, geographic distribution. We also seek representatives from small and large institutions and public and private institutions. In the case of small business applications, it is essential to have business and industry represented as well as academia.

It is very important that members of the scientific community perceive that their applications are reviewed fairly by people whom they recognize as being knowledgeable to the field and whom they respect as scientific contributors in that field. It is also important to ensure that we have an appropriately diverse spectrum of people.

The second critical element is how the study sections are organized: how they are put together and what research topics are reviewed in them. Science is changing very rapidly at this time. New tools are being developed and are being very rapidly applied to many different areas of biomedicine. Our study sections therefore

have to be maintained and kept up to date with the entier landscape of modern scientific research. We also have to accommodate newly emerging fields and new ways of doing scientific research.

To accomplish this, the Center for Scientific Review several years ago began a major initiative for systematically assessing and reorganizing our study section structure. We are slightly less than halfway through this process. It is being done with very broad input from the external research community. This effort has provided a very beneficial side effect of greatly improving interactions between NIH and the outside research world.

While reorganizing and updating our study section, the numbers and complexity of the applications we receive have increased enormously in the last few years. In order to handle this growth more efficiently, NIH has invested very heavily in new technologies. We are geared towards handling applications electronically, providing reviewers with CD–ROMs instead of boxes of paper and providing Internet-assisted review tools that we have developed and implemented.

Thank you for giving me the opportunity to present this information. I would be happy to answer any questions.

RESEARCH PROJECTS

Mr. REGULA. Thank you.

Is research generic? How do you decide which projects you're going to research? Is research for research's sake, or do you do research on specified medical conditions?

Dr. KIRSCHSTEIN. Each of the institutes has a mission which prescribes——

Mr. REGULA. So each of these individuals head an institute?

Dr. KIRSCHSTEIN. That's right.

Mr. REGULA. And within the confines of that institute, what they are researching is described or laid out?

Dr. KIRSCHSTEIN. Dr. Hanson, for example, is the Acting Director of the National Institute on Drug Abuse. This is to study substance abuse and addictive behavior, as he described.

We have another institute which you will hear from next week or the week after, on alcoholism and alcohol abuse. There is clearly an overlap.

In addition, as Dr. Nakamura from the National Institute on Mental Health tried to explain, such studies are in the neuroscience research area as well as pharmacology and chemistry. So there is overlap. But each of them has a defined mission. And each of them talks about the boundaries of that mission, and Dr. Ehrenfeld has described the boundaries of the study sections that will review them. They don't always have a one to one correlation between all the study sections and the Institutes.

So it's a very complex program that has grown up over the years. Because as I told you the other day, we started with one institute, gradually expanded and now we're up to 27.

NIGMS MISSION

Mr. REGULA. Dr. Cassman, what would be your area?

Dr. CASSMAN. The General Medical Sciences Institute looks at the fundamental molecular and cellular bases of biological proc-

esses. We do this primarily by looking at model systems, nonhuman systems for the most part.

So we're interested in the function of enzymes; we're interested in the mechanisms underlying cellular processes such as motility, the way cells move, as well as fundamental chemistry, biochemistry, and cell biology.

Mr. REGULA. How does that translate into action that affects everybody in this room?

Dr. CASSMAN. Let me see if I can give you an example. We have an investigator who has been looking at the mating of yeast.

Mr. REGULA. Yeast?

Dr. CASSMAN. Yes, yeast cells. Doesn't sound like it's going to be terribly important for anybody sitting around the table here—yeast cells, that's right. Just plain yeast cells. Mating behavior, of course, in yeast, is not at all similar to mating behavior in humans, so you can't use that as an analogy.

But it turns out that the signals that yeast cells receive when they undergo mating are translated into signal transduction processes, that is, into networks of intra-cellular behavior that are actually quite similar in all organisms, or at least all higher organisms.

But the interesting thing is that in the process of doing this study, he was looking into how cells transform, how yeast cells change from a benign form to a highly infectious form, such as yeast infections, which are very hard to deal with. He was able to identify a gene that was critical for the transformation and will, I hope, be able to lead ultimately to a diagnosis initially, and then ultimately for a therapy for these rather intractable fungal diseases.

Once this gets to the point of looking at the disease entity, we usually don't support it any longer. It's much more likely then in this case to be in the National Institute of Allergy and Infectious Diseases. The grant will move.

Mr. REGULA. The base of information?

Dr. CASSMAN. Yes, absolutely. And grants will move from our venue into some other institute's interest when they start being much more closely tied to a specific condition or disease.

Mr. REGULA. You could give a grant to Ohio State University to pursue the same research you are, or something comparable.

Dr. CASSMAN. Yes. All of this research is being conducted extramurally, that is, in the universities.

Mr. REGULA. You're just the manager of it.

Dr. CASSMAN. That's right. We manage the direction and the award of the grants.

Mr. REGULA. Make the selection of the applications that come your way, pick the 30 percent that are successful.

Dr. CASSMAN. Right. We do that together with the peer review process, of course. We also try to identify those areas that are on the boundaries of research and provide specific stimulus for those.

Mr. REGULA. Let's take the yeast. Was that initiated by your department or was it initiated by an outside group that said, we think this ought to be done?

Dr. CASSMAN. That's right. This is investigator-initiated research.

Mr. REGULA. Your department?

Dr. CASSMAN. Someone in the university who decided this was an interesting project. The peer review process validated that, said this was a good investigator, a good program and a good direction. And we supported and continued supporting it.

Mr. REGULA. Do all of you do some in-house research?

Dr. CASSMAN. Almost every institute except ours. The rest of them I think without exception, if I'm not mistaken.

Dr. KIRSCHSTEIN. And the National Center for Research Resources.

Dr. CASSMAN. Right. The two of us do not have intramural laboratories.

Mr. REGULA. You get your ideas from agencies or institutions that suggest we have, we meaning the institution, have an idea that we think could be beneficial to mankind?

Dr. CASSMAN. Right. And approximately 90 percent of all of the research that NIH supports is from outside investigators. It's not internal research.

Mr. REGULA. So you have a sizeable job just to manage these projects, I would suggest. How many projects would you have in your institute? How many research projects have you got working out across the country?

Dr. KIRSCHSTEIN. A total of 38,000 individual research grants.

Dr. CASSMAN. Not for us, but for all of NIH.

Dr. KIRSCHSTEIN. Yes.

Mr. REGULA. But collectively, the 27 directors——

Dr. CASSMAN. Twenty-seven institutes, right.

Mr. REGULA [continuing]. Manage these 38,000?

Dr. CASSMAN. Right.

Dr. KIRSCHSTEIN. The important thing about that management is that it is not purely administrative management. It is done by scientists who have chosen to become administrators who have really excellent scientific knowledge of these projects, so they can, as the project progresses, first of all, decide when it is important enough to something else to move to another institute, and secondly, to assess the science and whether it's going well and whether the budget throughout is consonant with the science.

Dr. CASSMAN. And we periodically, with the help of advisory committees, establish so-called RFAs, that is, requests for applications. We identify areas that are of high importance and where additional research is needed to try to stimulate areas, usually at the boundaries of the science.

Mr. REGULA. Mr. Obey.

IMPORTANCE OF PHYSICAL SCIENCES TO RESEARCH

Mr. OBEY. Thank you, Mr. Chairman.

Dr. Kirschstein, let me just ask you a series of questions and you can direct them to whomever you think ought to answer them. As biomedical research gets more and more complicated, it's obviously more and more dependent upon research done in other fields. Yet if you take a look at the President's budget this year, we have about a 16 percent increase for NIH versus about a 3 and a half percent increase for the National Science Foundation and the same story roughly for other scientific agencies.

I certainly don't expect you to argue against your own increase, but I do think it's appropriate for this Committee to be concerned, not just the Subcommittee, but the full Committee, to be concerned about the balance in our allocation of resources to different scientific agencies. Will you comment on some of the linkages that you have between NIH and some of these other agencies and give us some illustrations of why it's important not to neglect those other agencies if we want to have an adequate foundation for what it is that you do at NIH?

Dr. KIRSCHSTEIN. Mr. Obey, we could not agree with you more, that, as the science in general has become more complex, biomedical research is dependent on physics, chemistry, mathematics, biophysics, etc. There are enormous linkages, and we work as closely as we can with our colleagues in the other agencies. I think Dr. Cassman would be the appropriate person to address that.

Dr. CASSMAN. Yes, thank you. Yes, Mr. Obey, you're absolutely correct. The contribution of the physical sciences to biology has been immense, and it's been that way for many, many years, many decades, in fact. The most obvious way, of course, is through instrumentation, and Dr. Vaitukaitis mentioned a few examples. But there are many other forms of instrumentation with which I'm sure you're familiar, CT scanners, PET scanners, magnetic resonance imaging. All of those emerged out of fundamental research in the physical sciences.

In the basic research areas, there are equally a large number of examples. In fact, this is a good time to ask me, just yesterday I was at the Argonne National Laboratory for a signing ceremony where we, together with the National Cancer Institute, are establishing a facility at the Argonne synchrotron. That's a very large accelerator.

The interesting thing about this accelerator is that it is managed and built by the Department of Energy. There are six of those in this country, five out of the six are managed by the Department of Energy, one by the National Science Foundation. The interesting thing about the synchrotron is that when it was built, it was not at all with the intention of having anything to do with biology. It was for particle physicists who like to spin things around, little particles around at very high speeds.

Mr. OBEY. I like to do that with a martini. [Laughter.]

Dr. CASSMAN. Well, these go close to the speed of light, which is probably a little more than you're interested in.

And there is an interesting phenomenon, when you get close to the speed of light, these particles emit bursts of energy in the x-ray region, very highly focused, very powerful bursts of energy. In the 1970s, some clever people began to realize that these energy bursts, now, as far as the physicists were concerned, were a total waste. Because they were pouring energy into this machine to get things moving around, and the particles were just throwing it off.

This excess, really waste material as far as the physicists were concerned, was of fundamental interest to biologists and material scientists who could use it to do x-ray diffraction of the kind Judy was talking about.

So the technology borne of physics has been a critical element in the development of science. There are people who will say that the

major scientific advances have always emerged when a new technology is born.

But there is another aspect which probably will be more valuable in the future than in the past. We need physicists, mathematicians and engineers to do the mathematical modeling of complex systems, again, Judy mentioned that earlier, that most biologists are not trained in. These are highly complex areas. They require a great deal of specialized knowledge of mathematics and statistics.

For example, you asked about collaborations. Well, the Department of Energy is one example. Our institute has just established another collaboration with the mathematics division of the National Science Foundation. We're requesting applications in the application of mathematics to basic biological studies. We did this with the math division because they know mathematics. It's like Willie Sutton and the banks; you rob banks because that's where the money is. We went to the National Science Foundation because that's where the mathematicians are. We don't have that kind of contact and interaction with mathematicians that they do. And the collaboration helps both them and us.

That's just one example.

Mr. OBEY. So in other words, it would not be wise, if we want to further the long term development of biomedical research, if we focused only on funding NIH to the exclusion of the other agencies?

Dr. CASSMAN. In my opinion, I think it is essential that we provide significant funding for other agencies.

Dr. KIRSCHSTEIN. I think all of us feel that way. Dr. Vaitukaitis might like to respond.

OUTCOMES OF RESEARCH

Mr. OBEY. I've got a limited amount of time, so I'll take the first shot that each of you have. I want to keep it compressed if I can.

Outcomes research. The Agency for Health Care Research and Quality is cut 16 percent below the current year in the budget, with most of those reductions coming in the research on health costs, quality and outcomes program. Would you explain what the relationship is between NIH's mission and their mission? Where do you overlap? Where do you differ? Why is it important that they be funded, rather than just NIH?

Dr. KIRSCHSTEIN. It's extremely important to study the outcomes of, particularly, the clinical research that NIH has supported as it translates to the bedside, as we were talking about the other day, and then into the community. Our relationships with the Agency for Health Care Research and Quality are very close. In fact, as you probably realize, 75 percent of budget comes from the NIH evaluation, money.

We work closely with them. The Office of Medical Applications for Research relies on the Agency for Health Care Quality and Research to do the evidence-based literature searches that are necessary for us to draw on for our consensus meetings. Many of the institutes have projects which are collaborative. The National Heart Institute has for a long time worked with AHRQ in regard to studying whether a procedure which was used for years by the surgeons, to take patients with severe emphysema, that is, the lungs expanding, and whether by simply removing, surgically re-

moving parts of the lungs you could give them relief. Because the alveoli are expanding, people don't get as much air as they should.

Well, nobody had ever done a study to determine that. Between the Heart Institute and the other agencies there has been a very close relationship, collaborative funding and so forth. It is a very important thing to be doing.

RESEARCH MANAGEMENT AND SUPPORT

Mr. OBEY. I recall back in the early 1970s, we were rapidly expanding the funding for the Cancer Institute, but we were having a terrible time expanding the number of program officers to oversee the individual grants. Has your budget growth been translated into adequate resources for grant review and management? Example, has the number of grants handled by each program officer been increasing or decreasing? Has the number of NIH staff coordinating the peer review process been keeping up with the volume of the work? Or are we running into the same problem we ran into then?

Dr. KIRSCHSTEIN. We certainly have found that recently, as we have talked more about the need for the research management and support areas, with both the Department and with this Committee and the Senate Committee, that there has been an understanding that we need more individuals in those areas. So the increases have been generous.

Now, as Dr. Ehrenfeld points out, this is moving so rapidly that we really have to titrate it each year. But we are doing——

Mr. OBEY. I misunderstand something. You said the increases have been generous.

Dr. KIRSCHSTEIN. Yes.

Mr. OBEY. Which increases are you talking about?

Dr. KIRSCHSTEIN. In the research management and support for the various institutes and for then in turn, the Center for Scientific Review. That is in that RMS line that you put in the budget.

Mr. OBEY. So are you saying that in your estimation, the number of program officers have been increasing by an adequate amount?

Dr. KIRSCHSTEIN. Yes. I think we will have to titrate this as we go, in order to be sure that it is keeping up with our needs. Dr. Ehrenfeld described to you how rapidly things are progressing, and when she has those scientific review administrators, they have to do more and she may need more. They have to have new disciplines.

Dr. EHRENFELD. If I could just add to that, I think a very timely example is the new, very large initiative that we will be activating on bioterrorism. There is not sufficient infrastructure for reviewing these applications that are going to come in for managing the new applications that will be funded and implemented. It's an area that's going to require a great deal of regulation and oversight, because these are research projects and issues that have severe potential public health and public defense consequences and so on.

Dr. KIRSCHSTEIN. We have differentially increased the area of support for both the National Institute of Allergy and Infectious Disease and the National Cancer Institute, because both of them got very substantial increases this year. Primarily in the bioterrorism area which has, as you know, been increased remarkably and needed help.

LEVEL FOUR FACILITY

Mr. OBEY. I have a number of other questions but my time is virtually out. Let me just ask you one last question on this round.

The budget this year, as I understand, contains $105 million to construct the new level four facility at Fort Detrick. That is done to deal with severe biohazard problems. We had significant argument with the White House last year about whether or not that funding should be provided immediately. We were on the yes side.

I'd like you to lay out what is the status of existing NIH facilities with respect to their being able to handle bioterrorism related infectious agents and why it is necessary to build this new facility. I just want the record to have it clear as to why it's necessary.

Dr. KIRSCHSTEIN. Do you want me to do it now or put it in the record?

Mr. OBEY. Do it now, very briefly. I just want the record to show why that building is necessary.

Dr. KIRSCHSTEIN. There is an area at Fort Detrick where it will be possible to put this structure up. It is absolutely necessary. As new vaccines are developed for a new generation of smallpox vaccines and new generations of anthrax vaccine that there be the ability to do testing in animals as well as at the bench in order to be assured that challenges can't be handled, that we must have the protection of those facilities to do that.

Mr. OBEY. Would you explain also and expand for the record what is a level four facility?

Dr. KIRSCHSTEIN. Yes.

[The information follows:]

EXPLANATION OF BIOSAFETY LEVEL 4 (BSL–4) FACILITIES

Biosafety level 4 (BSL–4) facilities are designed to handle the most deadly agents and have exceptional engineering controls. BSL–4 facilities are highly specialized and are only operated in a few locations.

A BSL–4 facility is required for working with dangerous and exotic agents that pose a high individual risk of aerosol-transmitted laboratory infections and life-threatening disease. Agents with a close or identical antigenic relationship to Biosafety Level 4 agents are handled at this level until sufficient data are obtained either to confirm continued work at this level, or to work with them at a lower level. Members of the laboratory staff have specific and thorough training in handling extremely hazardous infectious agents and they understand the primary and secondary containment functions of the standard and special practices, the containment equipment, and the laboratory design characteristics. They are supervised by competent scientists who are trained and experienced in working with these agents. Access to the laboratory is strictly controlled by the laboratory director. The facility is either in a separate building or in a controlled area within a building, which is completely isolated from all other areas of the building. A specific facility operations manual is prepared or adopted. More information is available on the NIH web site. The address is: *http://bmbl.od.nih.gov/sect3bsl4.htm.*

Mr. OBEY. Thank you, Mr. Chairman.

Mr. REGULA. Just to follow up on Mr. Obey, does this have an element of involvement of the Defense Department?

Dr. KIRSCHSTEIN. Fort Detrick was once a facility that was run by the Department of the Army. Mr. Obey will remember that in 1971, a good portion of the Fort Detrick area was transferred to the Department for work by the National Cancer Institute, with the idea that we would no longer use it for the kinds of things they were doing at Fort Detrick.

However, the Army has kept some part of its activity related to organisms and toxins like anthrax, botulism, plague and ebola out at Fort Detrick. The National Institute for Allergy and Infectious Diseases will collaborate with them, and in this facility, the work will be done in collaboration.

Mr. REGULA. Will they pay part of the cost?

Dr. KIRSCHSTEIN. They have been paying the maintenance. I do not know what the details are. Dr. Fauci knows that. He can answer that for the record.

Mr. REGULA. They would not necessarily help pay for the new construction.

Dr. KIRSCHSTEIN. No. The new construction would not be paid for by them. We will pay for that.

Mr. REGULA. It would seem logical, if they're getting benefit, they should.

Dr. KIRSCHSTEIN. Yes. We will be working that out, and arrangements have been made. I will give you information for the record.

[The information follows:]

BIOSAFETY LEVEL 4 (BSL–4) FACILITIES

Lack of specialized, high containment labs, like the one proposed for Ft. Detrick, is the most critical factor that limits research on the most dangerous and highly-infectious pathogens. The Army currently has a BSL–4 lab on Ft. Detrick—it is one of only three operating BDL–4 labs in the nation.

The NIH lab to be built on Ft. Detrick is to address NIH's mission-critical requirements, which, although complementary, differs significantly from the requirements of the U.S. military. Protecting the civilian population requires a much broader range of research and the NIH lab will support research for all segments of the civilian population, including the elderly, children, infants, and people with suppressed immune systems caused by disease, therapeutic drugs or other reasons. Building this lab on Ft. Detrick, as compared to building it elsewhere, brings two distinctive advantages—it will facilitate cross-transfer of scientific knowledge and expertise between the scientific staff at NIH and the Army because of the co-location of the two BSL–4 labs: and the physical security of the lab will be enhanced because the lab will be on a secured military installation.

Mr. REGULA. Well, you tell them the Committee urges that the Defense Department contribute substantially to the cost.

Dr. KIRSCHSTEIN. Yes, sir.

Mr. REGULA. Mr. Hoyer.

SUCCESS RATES

Mr. HOYER. Thank you, I appreciate that.

Dr. Kirschstein, as you know, I have asked questions about pay line before, and we talked about review and how we get to the pay lines. My questions are, in a general sense, as we increase the funding substantially, first of all, is the science increasing in terms of the opportunities? In other words, is the quality of science applications from researchers around the country or around the world increasing at a significant level? And as we increase the pay line, what are we leaving on the table?

You might reference, I know there's still a, I guess you generally, in your first appearance, said between a 15 or thereabouts percent, and as high as 31, 32 percent pay line?

Dr. KIRSCHSTEIN. Even a little bit higher.

Mr. HOYER. You might want to reference that.

Dr. KIRSCHSTEIN. The science is increasing, as you heard from my colleagues, as you heard the other day, so rapidly. A great deal of it is due to this infrastructure we've been providing for years, both the instrumentation, general clinical research centers, the research training of beautifully developed scientists who all have remarkably wonderful ideas. So yes, the science is there to support the work and beyond.

Last year you may remember that although over previous years we had always talked about the fact that about one-third of the applications were what we wanted the success rate to be. Several of the institute directors, Dr. Fauci among them, said he would say that the science at a level percent of 45 percent could be supported.

Now, I don't think we anticipate that that is possible, nor should you under the circumstances that Mr. Obey has been raising. But certainly the science is there, and I think Dr. Ehrenfeld can tell you that her reviewers are making comments about the fact that the science is really excellent.

Mr. HOYER. I'd be interested in Dr. Ehrenfeld's observations, particularly as to how much science we're leaving on the table that peer review says would be very worthwhile to pursue.

Dr. EHRENFELD. It's hard to get hard data to support that. These are kind of subjective feelings. What we have seen, for example, are situations in which our reviewers are generally asked to try to identify the bottom half of the applications that they review. Those are in general not discussed in as much detail as the top half, because they're not likely to be funded.

It is getting more and more difficult to make any study section eliminate 50 percent——

Mr. HOYER. Distinction between the top half and the second?

Dr. EHRENFELD. They won't do it. Basically, the reviewers will rebel and say, I can put maybe 25 percent of these applications, sometimes 30, and say, these are okay to say, we're not going to discuss them in detail.

Mr. HOYER. How long have you been in your position, Doctor?

Dr. EHRENFELD. Five-and-a-half years.

Mr. HOYER. That's a relatively short time for some of us on this Committee, for a young timer. But in that time frame, have you seen the number that peer reviewers felt comfortable leaving on the table diminishing substantially? Even in that short period of time?

Dr. EHRENFELD. Even in that short period of time. It's anecdotal data, I don't have a good way to document that. But there is a clear perception in the community that the level of science that is being done and that is possible to do at this time has gone up enormously and is screaming for an opportunity. Having to turn back two out of three applications, because in the best of cases, if we have a 33 percent, two out of three applications will be rejected, that is hard.

Mr. HOYER. So it's pretty safe, from what you say, as a ball park, obviously, anecdotal, but a third, a third and a third. That is to say, about a third probably shouldn't be funded, a third has a good possibility and a third we fund. You said 25 percent, but I would just——

Dr. EHRENFELD. I would accept those numbers, they are as good as mine, yes.

Mr. HOYER. I would say to the Committee members, particularly who are new, that is a very substantially higher percentage of, that essentially is about two-thirds that are worthy of funding, which is way over the 40 to 45 percent that we historically say, so we think we've only been 10, 15, 20 percent on the table.

Dr. KIRSCHSTEIN. Actually, we historically thought getting a third was remarkably good. What we're seeing is that institute directors who have been here for a long time, Dr. Cassman, I, Dr. Fauci, are seeing significant increase in the quality and are saying, whereas we would have said a third, 45 percent is not out of line. That's halfway toward that second third.

DOUBLING THE NIH BUDGET

Mr. HOYER. I think the answer to the next question, then is self-evident. Obviously one of the issues is, we have now, assuming we adopt this budget, doubled in five years the NIH budget. The question that we've raised over the years that we've been doing this, are we able to digest this sum of money effectively?

Dr. KIRSCHSTEIN. Yes, sir.

Mr. HOYER. That's a pretty simple answer. None of us are shocked on this side of the table. Do you have concerns about that, though? I presume you have had concerns about that, and therefore that's been one of the issues, that we're not just shoving out money because it happens to be there.

Dr. KIRSCHSTEIN. We are not just shoving it out, and indeed, are making sure that what we are giving will be used well, that is, what the job is of each of the people at this table and those of their colleagues whom they have chosen very carefully to work with them, to be able to assure themselves that not only have the study sections and the councils done the appropriate job, but that monitoring and oversight is done well.

NEURONAL LOSS IN SCHIZOPHRENIA

Mr. HOYER. Dr. Nakamura, let me ask you a couple of questions. I'm always fascinated with these visuals. Obviously the objective of these visuals in this research is to prevent, ameliorate or cure. I was fascinated by the extraordinarily better diagnostic ability we have now in schizophrenia. What's the consequence of that? You mentioned that, I think, to some degree. Like that curing or ameliorating schizophrenia.

Dr. NAKAMURA. That is the goal. However, the results of this information will not allow us immediately to better either diagnose or treat schizophrenia. What it does is gives us a more profound understanding of how schizophrenia comes about. By knowing——

Mr. HOYER. What you're saying to me then is that with the color that occurs in the change in the diagnostic, I'm not sure whether that's a color or heat or what is that?

Dr. NAKAMURA. It's a color to represent a loss of neurons. The red represents a loss.

Mr. HOYER. There is no way to predict loss of neurons before it happens, only now to, in effect, see it?

Dr. NAKAMURA. Yes. Now we know, for schizophrenia, where neurons are lost in the brain and over what time period. So that gives us a signature that we can work from. It turns out that this

may have diagnostic utility. We don't know that yet for sure, because these are average data over a number of patients. But the number of these patients who showed the exact same phenomenon as individuals was striking.

So this may give us for the first time a signature, a physiological signature of the development of schizophrenia, which would make for a much better diagnosis than we've had.

RESEARCH ON CHILDHOOD MENTAL DISORDERS

Mr. HOYER. All of our time is limited, I want to go quickly. My colleague and I, in particular, Rosa DeLauro from Connecticut, have been very interested, as you may know, in post-traumatic stress disorder, particularly for children. We've talked to SAMHSA about it.

It is our premise that research on children's mental illness, obsessive compulsive disorders and others, bipolar, still lags behind in NIMH. Is that accurate?

Dr. NAKAMURA. Yes. The reason it lags behind is that children's behavior changes at such a rate, as we all know, that it has become very difficult to understand. For instance, we have a disease, diseases of misconduct or conduct disorder, for instance. We often get laughed at, because everyone knows who's raised children, there's going to be periods of misconduct.

We're talking about diseases in which these behaviors go on much longer than usual, and they're disrupting the development of those children. But because everybody has experienced periods of time when children are out of control, it becomes much more difficult to do an accurate diagnosis that this is a chronic condition in that child. And parents don't like to hear that these are chronic conditions in their children.

But as we have done longitudinal studies to know what are the outcomes for children with these kinds of conditions, we now know that the outcomes are very bad. But if we can intervene early enough, we can change the course of those children's outcomes into ones which are pro-social and useful for those families, so that they don't ultimately show depression, bipolar illness, etc.

NEED FOR CHILD MENTAL HEALTH RESEARCHERS

Mr. HOYER. Given that, does NIMH have a plan to strengthen this focus?

Dr. NAKAMURA. Absolutely. We have been working intensively with the pediatric and child psychiatry communities to try to train new clinicians who will do the research; to try and get psychologists who are interested in these areas to come over with new training programs. A new loan repayment program has been put into place with a particular emphasis on those working with children.

So we are working very hard to establish this, and we are trying to get researchers to work with particular groups of children, for instance, bipolar illness in children, to try and confirm those diagnoses, learn what the long term outcomes are. Most importantly, learn what treatments are most effective.

Mr. HOYER. Thank you. Mr. Chairman, do I have a chance for one more question?

Mr. REGULA. Sure.

CLINICAL LOAN REPAYMENT PROGRAM

Mr. HOYER. Dr. Vaitukaitis, I'm going to ask you a question, because you got cut off before. I really was going to ask you the question anyway. I was very interested in the Clinical Research Enhancement Act, or sponsoring it. I'm pleased to see that we're moving forward with the loan repayment program.

But my question is this. In the first year, as I understand it, only NIH researchers, researchers with NIH support, were eligible to apply. I don't believe that was our full intent. Can you comment on that? Do we intend to expand it? And what's the time frame of that?

Dr. VAITUKAITIS. This fiscal year, applicants were limited to those with support from NIH. Next year we will move into a more widely based approach that would include applicants with funding from other Federal agencies, the private sector, and probably even private donors. As long as the source of support for clinical research is peer reviewed, it can come from various sources. The loan repayment program would be considerably broadened next year.

Dr. Kirschstein may want to comment.

Dr. KIRSCHSTEIN. We're going to double the number of loan repayment contracts we give in fiscal year 2003. First of all, when the legislation was passed, it was a time in the budget cycle that we had to determine to use the money from other things, research programs, clinical research programs.

Secondly, except for a very small experience in the intramural program, we've never run a program like this. It involves having an individual contract between each one of the people who will receive the loan forgiveness, essentially. That's very labor intensive. It means you have to follow the people for years to make sure everything goes well.

We thought we ought to do it as a pilot program, carve out and do about 250 loan repayments the first year.

The second year, which is what we're asking for in 2003, we will double to 500, a little bit more, and——

Mr. HOYER. Expand the universe.

Dr. KIRSCHSTEIN. Yes.

Mr. HOYER. Thank you very much. Mr. Chairman, thank you, and Mr. Kennedy, thank you for yielding the time.

Mr. KENNEDY. My pleasure.

COURSE AND PROGNOSIS IN SCHIZOPHRENIA

Mr. REGULA. About losing neurons, that's in schizophrenia, right?

Dr. NAKAMURA. In schizophrenia, yes.

Mr. REGULA. If you watch the show, A Beautiful Mind, they come and go. So if they're gone, how do you get them back?

Dr. NAKAMURA. This is a particular form of schizophrenia. This is a form of schizophrenia that's childhood onset. This has a much worse course.

A Beautiful Mind is a great film, and portrays schizophrenia in a way which is much more realistic than in the tradition of movie making. However——

Mr. HOYER. Very diplomatic, Dr. Nakamura. [Laughter.]

Dr. NAKAMURA. It is not, it really isn't a typical case. You don't start out usually with a Nobel prize brain and come out of it as well as this individual has.

So it's fairly clear that this individual did not lose a massive number of neurons in the process. So we are talking about a special form of schizophrenia, it doesn't apply to all of them.

Mr. REGULA. So if you had a substantial loss, the hope for recovery would be very——

Dr. NAKAMURA. The prognosis for these individuals is very bad.

Mr. REGULA. I saw Dr. Nash interviewed the other day, and he seemed pretty much with it. He must have not lost too many to begin with.

Dr. NAKAMURA. There is a group of those with schizophrenia who undergo pretty substantial recovery and can work and can return to their families, if appropriately treated.

Mr. REGULA. Mr. Kennedy.

MENTAL ILLNESS AND HEALTH INSURANCE

Mr. KENNEDY. Thank you, Mr. Chairman.

A beautiful segue into my questions. If we know all of this, why don't we treat it like every other physical disease in terms of insurance coverage? Is it plain discrimination? Can any of you answer that for me?

Dr. KIRSCHSTEIN. Those decisions are not based on what we have determined. We provide the knowledge and we expect to and will work with the people who have to make those decisions. We work closely with the Center for Medical Services, the old HCFA. We have had discussions with health insurance companies. But that is not a decision that we can make, as individual scientists or as an agency.

Dr. BATTEY. But I think it is fair to say that psychiatric and behavioral disorders, have an underlying biological basis, just as deafness has an underlying biological basis, just as infectious disease has an underlying biological basis. So we do not believe that fundamentally these diseases are different than many other diseases that are covered by insurance.

Dr. NAKAMURA. Let me also say, the National Advisory Mental Health Council has indicated that there is no medically justified reason for differentiating between mental and other physical illnesses.

PROMOTING RESEARCH ON MENTAL ILLNESS

Mr. KENNEDY. Well, I appreciate your saying that. I think that we need to get about making sure that it's covered, then if it's a question of cost, then that ought to be a question of insurance, not a question of whether this is physical or not. Because they're blurring the two when they're discussing parity. I appreciate your comments and would invite you to give me any more when and if you ever get the inspiration to.

I'd like to say one other thing, though, about that. All of you here at the NIH are amongst the brightest, forward thinking folks. Yet, despite the evidence that four in ten of the top causes of disability worldwide, are mental illnesses, and when you measure the effective investment that NIH makes in mental illnesses as opposed to

other physical illnesses, for example, by using a recent estimate from the NIH, one finds that one dollar invested in mental health research for every six dollars that's invested in AIDS. So $1 for mental illnesses, $6 for AIDS, $1 for mental illnesses, $65 for cancer. One dollar for mental illness is the equivalent of $161.

So the fact of the matter is, we're not getting equal billing, even at the NIMH, or it's grown at a slower rate of growth than every other agency within the NIH. It seems to me, when we have the World Health Organization say mental illnesses are among the single greatest causes of disability worldwide, we ought to get more progressive leadership from the people that know the most. It's not going to happen from out in the hinterland. They don't appreciate what you appreciate. They don't have the education, the experience to know.

So we need it from you guys. And we're not getting it. I'm afraid to tell you, we're not getting it. The reason I don't think insurance companies are going to jump at the chance for parity, and this country is not going to jump at the chance is because the very people who know the most aren't doing what they need to do. You all may be restricted because you're part of an Administration, you can't speak out of turn.

But the fact of the matter is, if you don't speak, no one is going to speak. Because you all know that the stigma still rests around this country that mental illnesses are not physical illnesses. And you know that people are out there, who are not going to be pushing for this. Thank God for the movie, Beautiful Mind. It's the one popular culture movie that's now going to help penetrate people's consciousness about mental illnesses.

But you know what? We need more from you. And I'm really distressed to see that the NIMH does grow at a slower rate than all the others. I'm distressed that there's a fraction, that one of every hundred dollars that's spent on research goes to mental illnesses. I'm disturbed by the fact that we've got an elderly population that's going to boom and we have little to nothing invested in research for senior mental illnesses.

We just got a great presentation about how, when you grow old, it doesn't necessarily mean you lose all your neurons. Yet in spite of that testimony, we have inadequate funding for senior mental illness. It's not keeping pace at all, even within NIMH.

So NIMH is slower than every other agency, and then even within NIMH, senior mental illnesses are growing, the research into that is so slow. So I don't know whether it's a question of whether there's enough geriatric folks in this peer review group, but the grants aren't going out. I don't know if you could answer for me why there aren't enough grants being chosen in these areas, made in these areas in terms of peer review.

Dr. EHRENFELD. I don't know where to start. I can say a few words and I think Richard also wants to say a few words.

The solution sometimes to problems, even the most pressing problems, is not just to put money into it if the scientific opportunities are not there to make progress. Applications come in, the majority of applications that come in are investigator initiated. They come in from the scientific community, who get ideas and thoughts about ways to solve certain problems. That happens at a time when

there is a sufficient base of understanding of the illness or the disease or the problem, then we see applications coming in.

The peer review system can only review what applications it gets. And it's not so much there. That's the review side.

The institute side, I think Richard needs to address.

Dr. NAKAMURA. Yes. I accept your overall indictment that we have not been doing enough research in this area. This year, I have been very actively working to try and see what we can do. A key feature is that we don't have enough researchers in this area. So a couple of months ago, I met with the American Association for Geriatric Psychiatry and committed to renewed efforts in this area. We have started a number of initiatives, including a clinical trial to address psychotic illnesses. It's a major clinical trial with hundreds of enrollees to understand psychotic episodes in those who are older.

We have another effort too, on the loan repayment side, we're going to use some of our loan repayment money. More importantly, we've reconstituted the Aging Consortium to try and ensure that there is work across the institute and across agencies to try and address the problem of psychiatric illnesses in the aging.

BEHAVIORAL RESEARCH

Mr. KENNEDY. I appreciate that, Dr. Nakamura. I look forward to working with you on that. I'm sure this Committee does, too, because it seems to me that the baby boom generation is becoming a senior boom, and the highest rate of suicide is among seniors. We don't fully understand the complexity of evaluating and diagnosing the various mental illnesses that go hand in hand with growing old.

And just as you said, with children, it's hard for us to know, because kids are kids, how you're going to be able to determine what is bipolar or what is going to be obsessive compulsive or disorderly conduct. You can use the same excuse for seniors and say, well, they're old, and of course, they're supposed to be like that, just like children are supposed to be like that. And we both know both are false. Children do not have to be so ill, and we cannot relegate that to them just because they are children. Seniors don't have to be so depressed and ill, and then people just relegate that to a function of age.

So in both cases, I hope we work hard to continue to progress. But I know that's not going to happen unless we get a better—Secretary Thompson came here, didn't mention one word about mental health. And I know he cares about it. But it's clearly not coming from within NIH as a priority. Because the World Health Organization says it's the number one disabling, outside of cardiovascular disease, it affects every other aspect of the body, and we're not doing it. We're just not making the grade.

We know that behavioral health affects every other disease, we have them come up here and talk repeatedly about the need to address obesity and how we all need to get into healthier lifestyles and behaviors. Well, let's start addressing it.

That would be my last question, what are you doing in terms of the National Institute of General Medical Sciences to address behavioral science research within the different institutes?

Dr. CASSMAN. In an earlier question from Mr. Regula, it was pointed out that each of the 27 institutes and centers has a specific mission. The mission of the National Institute of General Medical Sciences is to understand the fundamental biological processes at the molecular and cellular level. And that's the level at which we are involved in behavioral science. We use primarily model systems to examine the genetic and biochemical mechanisms underlying behavioral phenotypes.

And I would point out that this is also true in a number of other institutes, the National Institute of Mental Health has programs in this area, the Neurology Institute——

Mr. KENNEDY. What are you doing, though, at NIGMS?

Dr. CASSMAN. We are looking at, for example, cellular processes that regulate uptake of antidepressants and antipsychotics. We look at drug-drug and drug-nutrient interactions that may lead to alterations in behavior, at specific enzymes and transporters in the brain that metabolize drugs and steroids and regulate their biological activity. This is the molecular level at which we investigate these things, like circadian rhythms, learning and memory and so on.

So we have a number of programs in each of these areas. Again, we look very carefully at what all of the institutes are doing. We try not to duplicate efforts in other institutes. And we look for regions in which we have specific expertise.

For example, the effect of anesthetics on memory and cognition. That's an area for which we have a specific program in anesthesiology. We focus on that within that area.

Mr. KENNEDY. I know this has been a legislative charge of both this Committee and the Senate, so I'd be interested in getting a more detailed description of what you've been doing.

Dr. CASSMAN. Sure.

[The information follows:]

BEHAVIORIAL RESEARCH AND RESEARCH TRAINING SUPPORTED BY THE NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

The mission of the National Institute of General Medical Sciences (NIGMS) is to support research and research training in the basic biomedical sciences. The projects supported by the NIGMS are in the most basic and fundamental areas of biomedical science and provide the foundation for subsequent disease-targeted studies supported by the other components of the NIH.

NIGMS supports behavioral research, using model systems primarily, to examine the genetic and biochemical mechanisms underlying behavioral phenotypes ("biopsychosocial" research, according to the NIH definition of behavioral and social sciences research). This includes research on:

- the neuron-to-neuron and neuron-to-muscle recognition necessary for appropriate connectivity in embryogenesis,
- sensory receptor production,
- neurotransmitter synthesis,
- receptor and ionic channel protein production,
- pharmacogenetics,
- muscular development,
- apoptosis,
- the structural biology of channel proteins and receptors,
- chemotaxis,
- the cellular processes that regulate uptake of antidepressants, antipsychotic, and anti-seizure medications from the intestine, their passage to the central nervous system, and their metabolism,
- drug-drug, drug-nutrient and drug-herbal interactions that may lead to alterations in behavior,
- specific enzymes and transporters in the brain that metabolize drugs and steroids and regulate their biological activity.

This research provides an understanding of the underpinnings of:

- circadian rhythms
- learning and memory
- sexual identification and reproductive behavior
- sensation and perception
- aggression
- pain and its management (including anesthetics' mechanism of action)
- the effect of anesthetics on memory and cognition
- the behavioral effects of drugs and steroid hormones
- addiction to psychoactive drugs or drugs of abuse

In NIGMS-supported research, model systems are often used to study highly conserved genetic mechanisms, metabolic pathways, and neurocircuitry. Such work has been demonstrated to be highly relevant to the study of more complex behaviors in higher organisms supported by other ICs at the NIH.

Research Training

Research training in the behavioral and social sciences is supported through NIGMS's Medical Scientist Training Program (a training program leading to the combined M.D.-Ph.D. degree), the Systems and Integrative Biology (SIB) training program, and programs of the Minority Opportunities in Research Division. All of these programs solicit applications for research training support in a broad range of disciplines, including the behavioral and social sciences.

For example, the current SIB grants fall into three broad areas of research training: neurobiology, physiology, and biomedical engineering. Support is provided for training in behavioral and cognitive neuroscience using multidisciplinary approaches to study the nervous system and the link between neural development, activity, and behavior. Included is research in sensory processing, sensory and cellular transduction, the biological basis of substance abuse and addiction, the neurobiology of stress, the neuropharmacology of social behavior, and the mechanisms of neurological and behavioral disorders.

In addition to institutional training grants, NIGMS also awards individual fellowships. Both the NIGMS individual fellowship program and the Pharmacology Research Associates Training Program provide support for fellows working in many of the same biobehavioral areas in which NIGMS provides research funding.

Mr. KENNEDY. And I thank you all for your great work to advance science in this country and help treat illnesses of our people. Thank you all very much.

Mr. REGULA. Mr. Sherwood would defer to you, Mr. Obey, you said you had a question.

EDUCATING THE PUBLIC ABOUT MENTAL DISORDERS

Mr. OBEY. Thank you very much. I just have two very brief questions I'd like to ask, one following up on what Mr. Kennedy has raised.

I am personally very disturbed about what we've seen happen in that Texas case just a couple of days ago with the woman who killed her children. I'm frankly appalled by the fact that a woman like that who obviously needed help as much as she needed it is going to wind up having to spend her entire life in jail. I guess as someone born in Oklahoma, that's something I've come to expect from Texas.

But nonetheless, I'm wondering what on earth we're going to do to overcome the primitive, ignorant indifference that this society has when it comes to mental illness. What I'm wondering essentially is, how can we do a better job of disseminating information about mental illness across the country in time to help people who actually need it, before you have tragedies like that? How can you get the information out that makes people understand that if you have this problem, it can be dealt with? What kind of work is NIMH doing with SAMHSA or on your own to try to get some of this information out?

Dr. NAKAMURA. We've been working very hard on this problem. I cannot comment on the particulars of the individual case.

Mr. OBEY. Of course not.

Dr. NAKAMURA. But our education outreach has been very, very vigorous. Getting the public's attention on any one issue, given all the problems that we have, has been very difficult. Perhaps the one silver lining to September 11th was the almost instantaneous recognition by all parts of the population that anyone could come up with a mental illness when put under that kind of strain and stress.

So we have been working very hard to put out publications, and I have a couple of examples here. We brought a number of packages. We had hoped to bring enough for everyone, however, I understand that getting packages into this building is extremely difficult right now. We brought what we could carry. There are two units here.

They show how we make available a number of different pamphlets on different kinds of mental illness. Here is a package with one page sheets, so that for individuals who want a quick summary of different kinds of disease conditions and resources for getting help, might be made more readily available.

We are also working very closely with the Substance Abuse and Mental Health Administration to try and bridge from the research side to the services side. Next week, in fact, a number of institute directors, Alcohol, Drug Abuse and NIMH, will be meeting with Mr. Charles Curie the Administrator of SAMHSA to talk about how we can bridge this gap between us even better. I think we

want to work hard on this and the American people deserve that kind of communication.

Mr. OBEY. Thank you. Just one last question—

Dr. KIRSCHSTEIN. We have enough of these packets to give to members of the Committee, if they'd like.

RESTRUCTURE OF PEER REVIEW GROUPS

Mr. OBEY. Thank you. One last question for Dr. Ehrenfeld. I understand that the Center for Scientific Review has been working to reorganize the structure of its peer review groups, and that you're looking at jurisdictions and boundaries of individual study sections. What are you trying to get done with this? Are you going to wind up with something that results in a more disease specific approach? Or are you trying to create more cross-cutting focus?

Dr. EHRENFELD. The first phase of this reorganization effort was really to decide on the best way to create broad clusters of review, really the macro level question that you ask. And the decision was made that we should have clusters of study sections that are based primarily on disease and organ system and the diseases associated with those organ systems, plus of course a set of study sections for fundamental discovery that potentially will apply to all possible diseases and organ systems, so the level of kind of understanding cellular processes.

That being said, each one of these clusters is now undergoing essentially an expert design of individual study sections that will populate that cluster. So if for example there is a cluster of study sections that will be related to cardiovascular science, experts from the research community in the broadest sense, dealing with all aspects, including behavioral science, now related to cardiovascular disease, basic science, and clinical efforts and so on are convened to sit down, look at the applications of today, hopefully with some insight about what's likely to be for tomorrow, and to design a set of appropriate study sections focused on cardiovascular sciences that will be able to handle with expertise and with fairness and with rigor the review of all the kinds of applications that come into the NIH dealing with various aspects of cardiovascular sciences.

This kind of organization is designed, you ask, what do we hope to accomplish by this. It's designed to acknowledge the fact that a time has arrived of molecular medicine, that is, a time when genetics, biochemistry, molecular cell biology, are tools that are being applied to virtually every area of biomedicine. It is designed to foster and support the review of new opportunities in newly emerging areas, bioinformatics, for example, bioengineering, new kinds of processes that we don't have study sections currently designed to review those applications, because those fields didn't exist five years ago.

But the science is changing so rapidly and the scope is increasing, that we want to make sure that we design a set of study sections that will be poised to review with fairness all aspects of science, all kinds of both hypothesis driven and most importantly, the multidisciplinary kinds of projects that are coming in to approach, to move things forward in the cardiovascular sciences area now requires research that integrates sometimes very basic research, sometimes the design of drugs to deal with the results of

that, the application to patient population to see the effects, to analyze the behavior aspects of whether it can work.

These are broad, multidisciplinary approaches and we need to have peer review groups that can handle that kind of scope.

So there were a number of concerns that people had about the way our current study sections were limited in review of applications for the future, and we want to make sure that we are poised, really, to look forward for research.

Mr. OBEY. What's the time frame and when will it be implemented?

Dr. EHRENFELD. It's progressing deliberately a bit slowly, because we rely on an iterative process and dialogue with the outside research communities. We're doing it in phases.

So I would say that the first new sets of study sections are likely to appear one year from May. All of these proposals have to be approved by the CSR advisory council and the next meeting is in May, and we will do the approvals for the first set of these IRGs. We give ourselves one year from that time to actually get it implemented in the study sections, formed and the reviewers appointed and so on.

And after that, it will continue for another two to three years.

Mr. OBEY. Thank you, Mr. Chairman.

Mr. Sherwood.

PUBLIC AWARENESS

Mr. SHERWOOD. Thank you very much. I'm enormously impressed with NIH, but I have a question that's going to be similar to my question of a few days ago. Dr. Kerry at the Institute of Medicine told us that they reported about a 15 or 20 year lag between the discovery of effective forms of drug treatment and their translation into routine patient care. As a businessman and a person that likes to get things done right now and see results, I think that's unacceptable. And I think you're doing all this wonderful research, but it seems needlessly long.

I want to know what we're doing to promote awareness of the findings of federally funded clinical research into effective drug abuse treatments. Dr. Hanson, would you chat with me about that?

Dr. HANSON. Certainly. You're very correct in terms of there having been substantial discoveries in neurobiology, underpinnings of addiction and the abuse process. We would like to see some of those discoveries translated into practice in terms of developing new pharmacological strategies and/or behavioral strategies for treatment.

There does seem to be this problem, and it's not just a drug abuse issue. It's a general neuroscience issue from some of these targets. We really are not positioned very well to develop drugs. We're not pharmaceutical companies. That's a very, very expensive proposition.

What we need to do is partner with institutions such as pharmaceutical companies and convince them that these are good targets to go after, that we need to develop new molecules that will actively interact with these biological systems. Then once we develop those molecules, we can take them back to our institutes, such as

Drug Abuse or Mental Health or Neurology and apply them to our specific issues.

We talked a lot about the neuroscience or neurobiological basis of mental health. That also applies to drug abuse, because drug abuse is in many cases a mental health issue. The substances interact with the same neurobiological systems that you see in schizophrenia, you see in depression, you see in anxiety. When we talk about stress, stress not only helps to precipitate mental illness, it helps to precipitate drug abuse.

As we identify these targets, if we can get this partnership going, we can develop drugs that will be useful across the span of neuroscience and neurobiology. That's where we are. We need to find ways to encourage these partnerships with the pharmaceutical companies.

Mr. SHERWOOD. Thank you. I'd like if I may to extend my question to the rest of the table. Because I don't think that it is only in drug treatment. I think it's in general medical advances.

As Mr. Kennedy said, with the baby boom population aging, there are other things, other than mental illness, that this becomes so important. We talked about diabetes and various. I just think that if we could stretch what you do a little bit, the delivery, we have to get your work and your knowledge down to Main Street. I think the system in this country is pretty slow at that.

I'd like your comments, and I'd like to see if I could start us thinking about what we can do about that. As a layman who understands very little of what you do, I think that's the issue that would be important.

Dr. KIRSCHSTEIN. We agree. Actually, we discussed this the other day with Chairman Regula, who gave us a very good idea, which we're going to implement almost immediately, about how we can get good diets out to people who are in need of that information who are elderly. The Chairman suggested that we put brochures and pamphlets in every Meal on Wheels tray that's deliver. I think that's something we will do. We have all that material, we spend considerable amount of effort and money to put those together. Each of my colleagues will be able to talk to you about that.

Dr. BATTEY. Yes, we are quite interested in the information dissemination. In fact, within the last few years, we have launched a campaign we call Wise Ears to inform the public about the dangers of noise induced hearing loss. We estimate that roughly 10 million Americans have lost significant amounts of hearing because of exposure to noise that could have been avoided. We guess that there's many more than that that are currently at risk right now.

The plain simple fact of the matter is, these folks don't know that, although it doesn't hurt now and they don't know they're losing their hearing, that they're accelerating the hearing loss process that accompanies aging by unnecessary exposure to loud noise. This is particularly true of individuals, for example, who come in with leaf blowers in your yard.

If you run a leaf blower for 15 minutes every weekend, you're not going to lose significant hearing. But if a person does it eight hours a day, five days a week, week after week after week, by the time that individual is 40, he may not.

Mr. KENNEDY. If I could interject, why hasn't the Department of Labor done something about passing regulations on noise?

Dr. BATTEY. There are OSHA standards, but——

Mr. KENNEDY. Yes, 30 years old.

Dr. BATTEY. They are old, and they don't typically apply to very small businesses. So your automobile workers are well protected, but individuals who run a gardening service, for example, don't have the same kind of regulatory protection.

Mr. REGULA. How about mechanics?

Mr. KENNEDY. Ear protection.

Dr. BATTEY. It's simple. It's preventable hearing loss that could stop millions of people from losing their hearing sooner. It's not rocket science, it's very simple.

Mr. SHERWOOD. Mr. Chairman, when you're mowing those huge pastures in Ohio, we'll expect to see you with earmuffs now. [Laughter.]

Mr. REGULA. That's music to my ears.

Dr. BATTEY. It's music until it gets over 80 decibels.

SCIENCE EDUCATION

Mr. SHERWOOD. I realize that maybe we've been talking about geriatric problems and mental health problems, but we also have, in diabetes and in lots of things, we have lots of health problems with young people.

Do we have a good program with the American public school system?

Dr. KIRSCHSTEIN. I think we do, but I think we could do better. We always can. Dr. Spiegel was here last Thursday, I believe, from the Diabetes Institute, and he will supply you with materials that we have.

[The information follows:]

PROMOTING HEALTH MESSAGES IN EDUCATIONAL SETTINGS

We agree that it is very important for children to learn about health issues and healthy behaviors, and that the educational setting can be an extremely important one for imparting messages that can lead to improvements in public health. This is one of the reasons that the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is working actively to spur research on the development of school-based programs specifically aimed at preventing or delaying the development of type 2 diabetes in children and adolescents, as part of our overall research efforts on early intervention and prevention strategies. In response to recent clinic-based reports and regional studies indicating that type 2 diabetes is becoming more common among children and adolescents, especially in African Americans, Hispanic Americans, Native Americans and Alaska Natives, and based on recommendations from a conference convened by the Diabetes Mellitus Interagency Coordinating Committee focused on this emerging problem, the NIDDK is developing a school-based initiative aimed at preventing type 2 diabetes in children and adolescents. The NIDDK is also targeting obesity--one of the major risk factors for type 2 diabetes in children. In fact, the increase in reports of type 2 diabetes among children parallels a similar rise in the adult population--as obesity has become a major public health concern.

Another NIDDK initiative that promotes the delivery of health messages in an educational environment is focused on tribal education of Native Americans, who are disproportionately affected by type 2 diabetes. In fact, some groups of Native Americans have the highest rates of diabetes in the world--with 50 percent or more of adults in some subpopulations affected. As in the general U.S population, type 2 diabetes is appearing at younger ages in Native Americans and Alaska Natives, largely due to the rising rates of obesity and lack of exercise. To combat these problems, the NIDDK is working in collaboration with Tribal Colleges and Universities to initiate the development of a school-based science education program that is centered on diabetes and will inform and motivate tribal children in order to develop their interest in pursuing careers in the biomedical sciences, and also improve their own health and that of their communities through education. Examples of areas to be addressed in this initiative include: (1) Tribal culture and science education within the context of diabetes; (2) involvement of the family; (3) building on the daily experience of Native American and Alaska Native children with diabetes in their communities; (4) the role of the Tribal elders in program development within the schools; (5) teacher training as part of the science development project; (6) implementation of the developed model programs in schools throughout Indian country; and (7) barriers to development and implementation.

In addition, through its National Diabetes Education Program--which it co-sponsors with the CDC and over 200 private organizations--the NIDDK has convened the "Diabetes in Children and Adolescents Work Group" to address the unique problems faced by children with type 1 diabetes and the increasing problem of type 2 diabetes in youngsters. A subcommittee of this group is developing a special "Diabetes in Schools Initiative" to reach educators and other professionals through the school system. Members of the subcommittee include representatives of the American

Diabetes Association, the Juvenile Diabetes Research Foundation, the American Association of Diabetes Educators, the U.S. Department of Education, the National Association of Elementary School Principals, the American Dietetic Association, the Centers for Disease Control and Prevention, the American Academy of Pediatrics, the National Association of School Nurses and the Indian Health Service. The first product of this initiative is the development of a science-based, consumer-friendly manual, "Managing Diabetes: A Guide for Schools," that will assist school personnel, children and their parents in managing diabetes during the school day. The manual will be disseminated through partnerships with organizations throughout the U.S. with special emphasis on promotion to the Nation's schools. The NDEP website (http://ndep.nih.gov) features additional information developed by NDEP under "Resources on Diabetes in Children and Adolescents."

The NIDDK is also seeking the most cost-effective means to translate to the U.S. population the extremely important prevention message of its recently completed multicenter clinical trial, the Diabetes Prevention Program or DPP. This trial demonstrated that individuals with pre-diabetes and at risk of developing type 2 diabetes can prevent disease onset and improve their blood sugar levels through modest improvements in diet and exercise. The DPP compared three approaches--lifestyle modification, treatment with metformin, and standard medical advice--in over 3,200 individuals with pre-diabetes. The DPP found that diet and exercise, which resulted in a five to seven percent weight loss, lowered the risk for developing type 2 diabetes by 58 percent. Participants lost weight by cutting fat and calories in their diet and by exercising at least 30 minutes a day, five days a week. However, we must now determine the best ways to translate these interventions--which were successful in individual adults--to the population at large or to segments of the population at particularly high risk for type 2 diabetes. As we move from efforts focused on the individual, such as the DPP, to population-based efforts, we will focus research efforts on demonstrating the value of delivery of interventions in community-based settings. For the pediatric population, this will include school-based settings.

The NIDDK is only one component of the NIH which is concerned about educating children with respect to health. For example, the National Heart, Lung, and Blood Institute (NHLBI) is particularly interested in developing and promoting ways to prevent obesity, which is associated with the development of type 2 diabetes, in children. Among its programs, the Institute supports work with multiple school districts to develop ways to prevent decline of physical activity in adolescent girls, to reduce obesity in Native American schoolchildren, and to reduce weight gain in African American pre-pubertal girls in order to prevent future obesity. With help from the National Recreation and Park Association and *Scholastic* magazine, the NHLBI offers a program, called *JumpSTART*, to help teachers and after-school activity coordinators incorporate physical activity and nutritional education into their curricula.

Dr. Vaitukaitis wanted to add to some of the things we've been talking about.

Dr. VAITUKAITIS. We have a science education program whose central purpose is to get information from NIH research to the lay public to help them make healthier lifestyle choices. For example, we have convinced the Boston Museum of Science, Howard University and Colorado State University to incorporate the recently announced findings from the diabetes prevention trial the exhibits that they already are working on that advise students about healthy choices in terms of nutrition. Colorado's program focuses on K through 6th grade students and follows them over that entire period to see if they are making healthy lifestyle decisions.

The Boston Science Museum exhibit focuses on the importance of exercise and appropriate nutrition to prevent diabetes, and uses multimedia, live interactive presentations by scientists, and has touch screen approaches to help educate the public.

We have about 30 science museums involved with this kind of approach across the country. We are going to modify the program so that we can work directly with NIH institutes who have health messages in order to take advantage of this creative source of talent that can get the information on health out to the public.

Mr. KENNEDY. If I could interject for a second, Mr. Sherwood——

Dr. KIRSCHSTEIN. We also have an office of science education within our intramural program. We know that there are activities all around the country. The advisory committee to the director will be meeting on June 6th, and we're going to have a group of high school kids come down from Boston to show us what they're doing at City Lab, for example.

Dr. Nakamura.

Dr. NAKAMURA. You had a question.

Mr. KENNEDY. My colleague is asking about how to get a bigger bang for the buck, as a businessman, from all the research that's going on. It seems as though we should step back and figure out what gives us a better bang for our buck in terms of our research dollar.

With respect to diabetes, for example, if you properly educate the kids and identify the risk factors and do a lot of prevention, this country would save itself billions of dollars in treatment costs down the road. Maybe you could comment on that with respect to diabetes.

Mr. SHERWOOD. Treatment and lost productivity.

PREVENTION RESEARCH

Mr. KENNEDY. If you could give us some feedback on what it costs for prevention versus what it costs to treat. It seems as though it is not even a close call. Why aren't we spending more of our dollars on prevention.

Dr. KIRSCHSTEIN. We are spending a great deal. Dr. Spiegel, who is the Director of the Diabetes Institute, talked about this at the session last Thursday. What everybody has realized is what you're talking about. What everybody has also realized is what Dr. Nakamura and you, Mr. Kennedy, have alluded to, the difficulty of doing this. We have a population of young people who are not in

the mode of walking and engaging in exercise. They are in the mode of sitting in front of their television sets and eating.

So what we are seeing is what used to be called adult onset diabetes occurring in children as young as nine and ten years old, and certainly a number of teenagers. We have a form of juvenile or young people's diabetes, which is unfortunately an inherited disease and for which we've made a great deal of progress, we know a lot about the genes, and we probably are on the cutting edge of doing something that will really help it. We know that we can prevent the onset of diabetes in young people, adult diabetes in young people, if we can break the way in which something happens.

We spend a good deal of money on diabetes research. It is $6 billion [CLERK'S NOTE: later corrected to $845,000,000]. You gave it a 15.6 percent increase this year, and a large amount of that is the diabetes education program, which we work on in conjunction with the CDC. That's been mandated by law. We have a great deal of money. But it is difficult to move it, and it's what you've been talking about.

Mr. WEEMS. Maybe I can add just a bit to this. This is a big concern of Secretary Thompson's, especially diabetes.

Dr. KIRSCHSTEIN. That's the prevention part.

Mr. WEEMS. This year in HRSA, he's formed a department-wide effort called Healthy Communities for diabetes, asthma and obesity, to leverage the resources of the NIH, the CDC, move into five communities, roughly five communities, and get an agreement from that community on actual targets for reduction of diabetes, asthma and obesity. So to become a grantee, we would ask the community for a target, then we would work with that community to achieve actual reduction targets in that area.

Mr. REGULA. May Mr. Sherwood and I suggest the communities that they should participate?

Mr. WEEMS. This will be a competitive process, but we always listen to any of your suggestions, sir.

Mr. REGULA. We'd have a little edge?

Mr. WEEMS. I think so.

Mr. KENNEDY. Mr. Chairman, I propose it for all those members that are currently present in the room. [Laughter.]

Mr. REGULA. Go ahead, Mr. Sherwood, you still have the time.

Dr. KIRSCHSTEIN. That was prevention research I was talking about. There's been much more than that on diabetes.

Mr. KENNEDY. Right. But it seems to me, Mr. Chairman, in my State, our public health Department works very closely with our insurance companies when it comes to inoculating our children. Because they get the money actually from the private sector, from the insurance companies, to do the inoculations. Why? Because the insurance companies know they're going to get saddled with the cost if they don't pay up front. So the Government acts as kind of the clearinghouse for that money.

Now, we have so much understanding and knowledge of behavior, how it affects health and how that health costs us money. We know about what research models work in terms of prevention and the like, but why don't we work with all this brain power here into formulating a model whereby we translate that and use our capitalist system of for-profit to fix our health care system. Then the

money would go into actually saving people's lives and keeping people healthy, rather than taking care of people after they get sick.

I think that this is part of the area that Dr. Sherwood is referring to. That's what we need: prevention. We need health promotion, not sickness care.

What are you doing to get our health insurers to do that?

Mr. REGULA. You heard it, Mr. Sherwood, Mr. Kennedy is on record in favor of the capitalistic system. [Laughter.]

Mr. KENNEDY. I think it's a legitimate question. Because if we don't figure out in a way, we're just putting a ton of money behind very unsuccessful, costly health care or sick care, versus putting our money behind health care. If you can suggest to us ways that we can, it seems to me if the private sector knew this stuff and we could figure out a way for them, we could show them, you and the scientists could show them, here's how you make the money. If you do this, you're going to have a bigger profit.

Why can't you do that?

INFORMATION DISSEMINATION

Mr. REGULA. I think this goes back to Mr. Sherwood's original contention, you need to get the material out, and you're saying to the private sector, so they can make use of it.

Dr. KIRSCHSTEIN. We're getting the information out. We can always do a better job with that. We have had discussions with the health insurance companies and we have had some evidence that several things are happening.

One of the things that is working well, and I think it is again a tribute to the Department and to the Secretary, is that we now have coverage of clinical trials, particularly in cancer chemotherapy, by the Medicare system, so that people can be on the best trials for the situation that they find themselves in. We have been working for years to try to get that done in regard to private health insurance, and frankly have not made much progress.

Mr. KENNEDY. We don't do it in the public health care sector. For example, chemotherapy, with prostate cancer, one of the most successful things is this Brachytherapy type of therapy, which is the isotopes that they implant. It's costly, but when you look at the overall cost of chemotherapy plus surgery, it's incredible. Do you think Medicare is changing its reimbursements to accept it? No. Why? Because the money is behind the cutting and the surgery, and the money is behind the chemotherapy.

We have the science, the data is in. They use their own data at CMHS or whatever it's called now, CMS. So it's not working. We're not breaking through. I think my Republican friends would be very disappointed to know that this Republican Administration is funding inefficiency when it comes to cost outcomes and effectiveness when it comes to treatment, in our public system.

So how are we going to convince the private sector to make the changes? We're not even willing to do them within the Medicare and Medicaid system.

Mr. REGULA. Mr. Sherwood for the defense. [Laughter.]

Mr. SHERWOOD. I am very interested that Mr. Kennedy just sort of endorsed the HMO model.

Mr. KENNEDY. I do endorse the HMO model, in the ideal sense of managed care, I endorse it wholeheartedly. Although in its practice it's never been more than managed cost. And that's not managed care.

Mr. SHERWOOD. Well, but we need to have managed care. And we need to have healthy practices for good outcomes as opposed to expensive treatments later. We all agree with that.

I'm not sure they want to listen to us any more, although you sound a great deal like my brother, the Doctor Sherwood when he gets going on this.

I think we've made it very clear to you that from two ends of the spectrum a little bit on where we stand ideologically, that we agree very much that we think, as great as your work is, we're inefficient in getting it down to the end user.

Dr. KIRSCHSTEIN. I would agree with you.

Dr. BATTEY. I think we all agree that it would be better to prevent disease than to treat after disease ensued. But the issue of prevention and changing people's behavior and habits is a very difficult affair. My 15 year old son can tell you that fatty foods are not good for him and that he ought to get up off his backside and go out jogging rather than watch TV. And he'll tell you that while he's trundling off in the car to McDonald's to buy a Big Mac and a bunch of fries. It's very difficult.

In fact, the Cancer Institute and a number of others have spent, I don't know how much money, but a lot of money on an anti-smoking campaign.

Mr. KENNEDY. In Rhode Island, we've had great success showing that there are proven models to successful smoking cessation. Behavioral models, I might add.

Dr. KIRSCHSTEIN. Mr. Kennedy, to some extent that is true. We have not had great success in all our young people. The most difficult problem we have is with young, adolescent girls. Because they are not stopping smoking the way our young men are, and they are concerned because there is a myth that if they don't start to smoke, or if they're already smoking and they don't stop, they will gain weight. It is something that we have been concerned about and we have had campaigns out for at least 20 years, when I first started doing things about women's health.

Mr. REGULA. That's very true.

Mr. KENNEDY. I would say, though, the success we have had in this prevention is probably as meaningful as any other success we've had in the whole cancer area. Because when you look at the savings down the road——

Dr. KIRSCHSTEIN. It's hard, as Dr. Battey says, and what's hard takes convincing. We've worked at it and we haven't——

Mr. REGULA. Because fries taste better than carrot sticks. Bottom line. [Laughter.]

Dr. BATTEY. Unfortunately, the human organism is adapted to an environment of 40,000, 50,000 years ago when we were hunters and gatherers and we ate anything we could get our hands on, because we didn't know when we were going to eat next. The body simply has not had time enough to evolve to a modern world. The instincts that served us well way back then are now serving us very badly.

Mr. REGULA. Do you have any further questions, Mr. Sherwood?

Mr. SHERWOOD. We've run the gamut. [Laughter.]

Mr. REGULA. Mr. Higgins advises me that in the case of juvenile diabetes, I guess the insurance companies are recognizing that this is cost savings to them——

Dr. KIRSCHSTEIN. Yes.

Mr. REGULA [continuing]. To persuade people to change their dietary habits.

Dr. KIRSCHSTEIN. I hope so. That's a good start.

DRUG PREVENTION

Mr. REGULA. That's perhaps a model. Are we having any success with drugs? Does your work reach out to drug prevention?

Dr. HANSON. They just gave the example of tobacco cessation. We have seen a decrease in tobacco use by young people. A lot of prevention work is going to be targeting adolescents and young people. When they start to pick up those habits, whether they be tobacco or they be other substances of abuse, and they do it when they're young, they become entrenched in that habit.

I showed you that graphic where there is actually a change that occurs in the brain, in the way it processes information from when they start using drugs, they're driven by the reward, the feel good phenomena of the drugs, but then things change, and now a motoric system, a system that drives habit and compulsive use takes over. When you ask people that are using drugs for long periods of time, "do you enjoy this?; why do you use the drug?", oftentimes they'll say, "I hate the drug, I would do anything not to smoke." But the urge is so intense that they can't resist it.

We have to figure out, what does this mean? Why is the brain changing in the way it processes information and why are young people vulnerable early on? We know that young people don't make good decisions sometimes. There are some interesting neurobiological development studies showing that there are things that take place in the frontal cortex, the front part of the cortical structure, that are developmental and probably underlies the issue of why they don't make good decisions.

Now, if we can understand these mechanisms and develop strategies for developing and maturing that decision making process, we'll go a long way to dealing with drug abuse, diabetes, anything that has to do with decision making. This is an underlying theme, and we can manipulate it.

CRAVING

Mr. REGULA. You're suggesting that maybe research will lead us to ways in which we can alter this craving, if you will?

Dr. HANSON. Exactly. Alter it or understand what's going on. Then maybe work with our education system in such a way that we help to develop the skills for better behavior and better decision making.

Mr. REGULA. That would be an enormous breakthrough, wouldn't it?

Dr. HANSON. Exactly.

Mr. KENNEDY. Mr. Chairman, in the genome project, I think they've identified some areas where it's hereditary, and they can actually be able to predict which people have a higher propensity to fall into addictive disorders.

Dr. HANSON. Exactly. There's a lot of overlap not only in terms of substance abuse and addiction, but also in terms of not making good decisions about lifestyles and not making good decisions about education. So it just falls right through the entire spectrum of behavior.

Mr. REGULA. Seems to me you all have a lot of challenges. Any further comments, questions? Thank you all for coming. It's a provocative discussion. With this, as with previous ones, I wish America could sit in via C–SPAN. It would be a tremendous education for the public to understand what's happening.

NIH is somewhat of a well kept secret. If I go down the street in Navarre, Ohio, or any city and say, what's NIH, you'd get very many positive answers, probably not a lot.

Dr. KIRSCHSTEIN. We would be pleased to visit any of your districts at any time.

Mr. REGULA. I understand that. But it does, the message doesn't get out. The first lady in Ohio is very immersed in drug efforts, but I think you make a thought provoking notion that we could deal with this by altering mental behavior. How to do that, of course, is probably still a locked up secret that you're seeking.

Dr. HANSON. But we're learning a lot about it. There are some substantial inroads into understanding what that process is, and maybe even how to manage it.

Dr. NAKAMURA. As well as using social behaviors in order to influence the behavior of people. We are learning a lot on how to change human behavior just through social influence.

Mr. REGULA. By peer pressure.

Dr. NAKAMURA. Absolutely.

Mr. REGULA. That seems to be a very significant part of what's happening. We're dealing with this in education, to get kids to stay in high school. Because I think peer pressure is what oftentimes persuades them. They just announced a $31 million project in Ohio funded by the Gates Foundation and the Ford Foundation and the Knowledge Works Foundation. I think one of the keys to that will be able to deal with peer pressure.

I'm dropping out, I'm going to get a job. His pal says, well, I'm going to drop out, too.

Dr. KIRSCHSTEIN. We have been partnering with the Gates Foundation to do a number of activities related to the things NIH is involved in.

Mr. REGULA. Is that right? So much to do. Thank you for coming.

Dr. KIRSCHSTEIN. Thank you, sir.

Mr. REGULA. Hearing is adjourned.

INFORMATION TECHNOLOGY IN BIOMEDICAL RESEARCH

Mr. Regula: With the increasing pace of new developments in biomedical research, I assume this means there is a greater need for enhanced information technology, such as more sophisticated computer programs and data storage systems. Are you able to keep pace with these new demands?

Dr. Cassman: The completion of the human genome project marked the beginning of a new era in biology—a data rich era where fundamental discoveries will be made by "mining" the vast amounts of data amassed from genomics, proteomics, structural genomics, pharmacogenomics, etc. A key to all of these discoveries is the efficient storage of data in ways that facilitates their retrieval. Through the NIH-wide consortium Biomedical Information Science and Technology Initiative (BISTI), the NIH is strongly encouraging proposals to manage these data, all the way from the laboratory notebook to the incorporation into databases. The NIH, through its BISTI initiatives, as well as others, is also seeking to attract scientists into biology from quantitative disciplines such as computer science, physics, mathematics, and engineering. Specific examples include the mentored career development award, post-doctoral fellowships in quantitative biology, and the joint National Institute of General Medical Sciences/ National Science Foundation Biomath initiative. With respect to the latter, 90 proposals were received this past year and 20 are scheduled for funding. Covering the areas of both research and training, two institutes, the National Institute of General Medical Sciences and the National Human Genome Research Institute, have announced Center's of Excellence Programs in computational biology. Several proposals are slated for funding this fiscal year. These centers will effectively bring together scientists from the quantitative disciplines and the biological disciplines to tackle problems of computational biology, including data storage and data analysis.

Mr. Alan Graeff, Chief Information Officer, CIT: Appropriate use of enhanced information technology facilitates and accelerates advances in biomedical research. Such technology will combine new hardware (e.g., faster processors, parallel computers, network access and storage, faster and easier communications between researchers) with increasing sophisticated software to take advantage of technology (e.g., the development of new computational algorithms, high performance methods, better data mining, and efficient access to extremely large databases). In order for NIH to keep pace with new demands, we must have access to new technology (both software and hardware) as well as the necessary skilled personnel to take advantage of these new opportunities.

Dr. Nakamura: The area where neuroscience, information technology, and informatics (including computer programming) overlap is rich with scientific and technological opportunities. Essential to making the most of these opportunities, however, is the close collaboration among experts from these three contributing fields—the technology and its implementation must be intimately familiar with the scientific domain it serves. It is key, therefore, that neuroscientists are involved closely

in the development of the information technologies and informatics approaches that are meant to acquire, analyze, share and store the data generated in their labs and clinics.

For more than a decade, NIMH has been at the forefront of bringing these fields together to advance the understanding of the brain in health and illness, and these efforts are starting to pay off with better and more efficient ways to make sense of this most complex organ. As these informatics approaches become more sophisticated, their impact on the way we study the brain and conceptualize its workings have grown tremendously. This, of course, stimulates the development of new informatics tools and approaches, which, in turn, generate new insights about brain function. In short, research collaborations across the fields of information technology, informatics, and neuroscience has greatly enriched all three of these areas. NIMH has invested in this area with considerable thought and consultation among key stakeholders.

Dr. Hanson: Meeting the IT requirements of biomedical research means creating an informatics infrastructure that supports NIDA's clinical trials and capture of associated clinical data. Advances in computing, storage, and communications provide new opportunities in such medical informatics areas as data and knowledge capture, building of decision support tools that aid in analyzing clinical information and assist in clinical decision-making, information retrieval, and integration of disparate information sources.

Dr. Vaitukaitis: NIH is working to substantially increase IT investment in biomedical research, especially in areas designed to cope with the enormous amounts of data that are being generated by high throughput technologies and the need to quickly process and analyze that data. NCRR has moved rapidly in the past several years to develop web-based technologies to enhance access to sophisticated research tools for modeling and simulation, data storage and retrieval, and sophisticated visualization software.

Mr. Regula: What is each of you doing to address these increased needs?

Dr. Cassman: The institutes and centers are addressing this demand for enhanced data capabilities in a number of ways. Last year, NIGMS established a Center for Bioinformatics and Computational Biology that will fund projects both to store, retrieve and manipulate biological data and to mine these data to advance the newly emerging field of biological complexity. NIGMS expects to devote about $40 million to these projects.

Mr. Graeff: A number of research projects combine enhanced information technology with the specific collaborative needs of the intramural research program. For example, research programs are involved in the quantitation and visualization of medical images from many medical modalities, computational methods for the analysis of management of genetics data, implementation of advanced telemedicine technology, providing expertise and specialized hardware for use in molecular modeling and

computational chemistry, developing parallel algorithms for a number of complex problems including the multivariate measurement of gene expression relationships, and the design and development of a large image archive system which will facilitate the analysis and sharing of the results from major imaging studies. Recent infrastructure enhancements in the intramural program have focused on enlarging the capacity of Beowulf-class supercomputers and Storage Area Networks, and on upgrading the NIH campus network to support transmission of medical images and other large data files.

Dr. Nakamura: NIMH continues to lead an initiative called the Human Brain Project, which supports research and development at the interface of information technology, informatics, and neuroscience (also called neuroinformatics). This initiative, which was launched about ten years ago, has a broad programmatic thrust that covers a wide range of neuroinformatics topics. The Human Brain Project is supported by 14 federal research funding organizations from across four agencies (NIH, NSF, NASA and DOE). Activities supported by this initiative include research grants, grants to support the training of new investigators, conferences and workshops, and efforts to coordinate neuroinformatics research at national and international levels.

In contrast to the long established and very broad Human Brain Project, in 2001 NIMH and NINDS jointly launched the Neuroimaging Informatics Technology Initiative (NIfTI), which is highly focused on informatics used in neuroimaging research. Neuroimaging research is key to understanding human brain function, and informatics tools are paramount to the way neuroimaging research is conducted. A concerted effort to advance informatics in this particular area has the promise of significantly advancing knowledge about the healthy and disordered brain. NIfTI has five specific objectives: enhance existing informatics tools, disseminate those tools to researchers who need them, address common issues such as interoperability of data and tools, provide unique research training opportunities, and support research and development of the next generation of informatics tools for neuroimaging research. These objectives are being pursued with close consultation with the field through scientific workshops, conferences and electronic fora.

NIMH also plays a prominent role in the development of new informatics tools for better analyzing and understanding gene expression in the brain. Building upon the foundation of gene sequencing efforts of the last decade, an important goal for this decade is to know which genes are expressed in which parts of the brain at which times across the lifespan. Arriving at this answer requires integration of information from laboratories carrying out genetic research, histological analysis, and brain imaging. In addition, to assure that these tools are widely available to and useable by the research community, NIMH, along with the NIDA and NINDS, has conducted a series of scientific workshops to guide federal efforts in this technology development.

NIMH is an active participant in several other information technology and informatics initiatives across the NIH. These include the Insight initiative, which is led by NLM. Insight supports scientists from academia, small business and industry to

develop – in a coordinated fashion – software tools for using image data generated by biomedical imaging instruments, as well as developing a community-based computer programming protocol that results in robust and testable software. The new programming approach has the potential to address several obstacles currently impeding progress in scientific informatics (e.g., lack of interoperability of software tools, difficulty in validating those tools, and lack of coordination across different laboratories that modify existing software tools). NIMH also has worked with the NCRR to develop and, now, implement the Biomedical Informatics Research Network (BIRN). The BIRN is developing information technology strategies and informatics tools to give biomedical researchers a new way to quickly share and analyze clinical and basic research data. NIMH participates in an initiative to provide the research community a database of protein sequence data. This database is necessary to allow biologists to use the enormous amount of data from the Human Genome Project and from structural and functional genomics projects to understand human disease, and to develop drugs to treat disease. NIMH also is involved with the Biomedical Information Science and Technology Initiative, and supports research grants that have been solicited through that initiative.

Of course, NIMH also supports research in information technology and informatics that are related to brain and behavior through grants that were not applied for through special initiatives or solicitations. Most of these investigator-initiated applications (and grants that result from them) are housed in the Neurotechnology Program, the Small Business Innovation Research Program, and the Small Business Technology Transfer Research Program.

Dr. Hanson: NIDA has built a clinical research informatics infrastructure to supply systematic bioinformatics support and integration of NIDA's diverse research initiatives. Within this framework, we are developing the innovative tools required to connect scientists and clinicians with necessary information for the testing of new treatments, both pharmacological and behavioral. In 2002 and 2003, we will continue to establish informatics applications with standardized data for use by all NIDA staff.

The repositories for clinical basic research documentation results in storage and networking needs growing at about 30-50 % a year. This poses a challenge to IT offices which constantly need to assess their data and network capacities and requires that systems and infrastructure development be modular so that growth and changing demands can easily be accommodated. Meeting these needs has been accomplished through systematic planning and development which involves both NIDA staff and researchers as well as outside expertise.

Dr. Vaitukaitis: NCRR is investing in infrastructure necessary to assure high speed internet access of biomedical research centers to data distributed at many sites throughout the country and to aid communication between researchers. Several of NCRR's Biomedical Technology Resources are devoted to development of software platforms that permit integration of many disparate software tools for data mining and

display. These tools are widely available to the research community and mechanisms for dissemination, support and training related to them are in place. We have a new initiative aimed at providing infrastructure necessary for construction, use and maintenance of federated databases that will become the normal access to biomedical data in the future.

NEW TECHNOLOGIES

Mr. Regula: When a new technology is discovered, how are researchers informed of the new technology and how do they get trained in its use?

Dr. Kirschstein: A significant component of each NCRR Biomedical Technology Research Resource is devoted to the dissemination of new technology and the training of researchers in its use. This distinguishes these resources as infrastructure investments from research project grants. The resources run workshops at national meetings, offer specialized short courses at locations throughout the country, and publish and present recent technological advances in a wide variety of technical venues. Increasingly the internet has become the medium of choice for interactive communication with potential users. Every resource maintains a complete web site with software that can be downloaded and tutorials tailored for both naive and sophisticated users.

NIH REAUTHORIZATION

Mr. Regula: The last comprehensive reauthorization bill for NIH was the NIH Revitalization Act of 1993. What impact has not having a more recent authorization bill had on your ability to develop a strong infrastructure and put mechanisms in place to effectively handle a doubling of your budget?

Dr. Kirschstein: NIH has longstanding authorities in the Public Health Service Act that permit the agency to continue activities related to its mission in the absence of specific reauthorization legislation. Thus, the lack of a recent omnibus reauthorization act has not impeded the progress of our work. In addition, since the 1993 law was enacted there have been more than a dozen authorizing bills enacted, providing additional mandates, new Institutes and Centers and specific authorities for the Agency. With the help of the Administration and the Congress, NIH has maintained its ability to develop a strong infrastructure and to ensure that mechanisms exist to enable appropriate expenditure of funds provided through the doubling effort.

LEGISLATIVE ASSISTANCE

Mr. Regula: Are there areas where you could use some legislative assistance?

Dr. Kirschstein: At this time, NIH does not have any legislative proposals that have been reviewed within the Administration and are ready to be transmitted to the Congress.

MULTI-YEAR FUNDING OF RPGs IN FY 2003

Mr. Regula: The President's budget includes a language request to allow for full funding of NIH grants. If we were to agree to this request, what would it mean for your Institute? How would you use this authority?

Dr. Kirschstein: Over the last five years, NIH's Budget has experienced a large infusion of resources. As we prepare for the outyears, we are pursuing multiple funding policies that will allow us to manage our resources effectively by providing maximum flexibility to fund priorities in the outyears. It is possible that the full funding of research grants will provide this needed flexibility. Full funding will allow for the upfront payment of research grants, thereby reducing NIH's outyear mortgage – the commitment to fund non-competing grants in future years. If the full funding of grants proves to be an effective financial tool, we will need authorizing language in FY 2003 to implement this policy.

The effects of implementing a full funding policy are dependent on multiple variables, including dollar amounts for new and competing grants and the average costs of grants. For example, with full funding in FY 2003, if NIH chooses to keep the same dollar amount for new and competing grants as in the request we would decrease the number of these grants to offset the increased average cost per grant. Any decision will be made in the context of what is best for NIH as we prepare for the outyears, as well as what is the best policy to maximize the breadth and depth of the NIH research portfolio.

RESEARCH TRAINING

Mr. Regula: What is done in the private sector, both at colleges and universities and at other private entities to enhance the training of biomedical researchers?

Dr. Cassman: Graduate universities and medical schools throughout the country provide training for aspiring biomedical researchers at the predoctoral level. This training takes 5 to 7 years and culminates in a Ph.D. or M.D.-Ph.D. degree. Students participate in organized programs under the supervision of research faculty. During this period, they take courses, laboratory training, and complete a major research project under the supervision of an experienced research mentor. Predoctoral students receive financial support from a variety of sources, including the universities themselves, foundations, and the NIH.

Research training at the postdoctoral level takes place at these same institutions, as well as other centers of research activity – including research institutes, government laboratories, industrial laboratories, etc. This advanced training is much more

individualized, with the postdoctoral scientist working closely with one or more established scientists on a research project.

RESEARCH INFRASTRUCTURE

Mr. Regula: What is done to provide adequate infrastructure for investigators to work in?

Dr. Vaitukaitis: The NCRR supports nationally distributed resource centers for clinical research, biotechnology, and animal research, which provide infrastructure to facilitate the research of NIH-supported investigators, with a critical mass of the necessary expertise to address complex biomedical research. In addition, the NCRR awards grants for expensive, state-of-the-art instrumentation to be shared by a number of investigators. Construction grants and grants for the renovation of animal facilities are also awarded by NCRR, to provide the bricks-and-mortar infrastructure to assure that investigators have access to modern research facilities.

GENOMICS AND GENETIC MEDICINE

Mr. Regula: In the post-sequencing of the human genome era, what role will NIH have in the field of genomics and genetic medicine as it relates to training and infrastructure? How do you see this role changing in the future?

Dr. Kirschstein: In the era following the sequencing of the human genome, the challenge will be to fully interpret the information embedded in the sequence. Although we know much, more remains to be understood. Significant investments in both technologies and manpower will be required, particularly in bioinformatics and computational biology. Bioinformatics provides the tools for extracting meaning out of large volumes of data, and is essential for the next phase of biology.

Other large databases about the genome need to be generated – including the sequence of the genomes of several additional model organisms (especially mouse, rat, zebrafish, chimpanzee, chicken and others), a full description of how human variation is organized across all the chromosomes, a complete set of gene products, and a global understanding of how genes turn on or off, and how that is altered in disease states.

Simultaneously, there is a need to look at the way biological systems are organized and how the organization is linked to function. The information from the genome is a necessary prerequisite, but we also need to understand how the components function together and how they behave as dynamic systems, which can respond rapidly to the environment. The technology and concepts of proteomics are a part of this next level of understanding, as is the development of trained scientists who can manipulate the mathematics and engineering concepts needed to model complex biological systems. This research will be a central theme of biology in the future.

NIH has developed a number of training and career development programs to stimulate the training of scientists who have the multidisciplinary skills that will be required in this new era. The agency is also mindful of the need to recruit individuals from underrepresented minorities into this field and is supporting programs with that goal. In addition, there will be increasing support of infrastructure such as databases and other common resources, including technology development to make the research more efficient and cost effective.

CENTER FOR BIOINFORMATICS AND COMPUTATIONAL BIOLOGY

Mr. Regula: NIGMS established a new Center for Bioinformatics and Computational Biology in May of last year. Tell me more about this Center including what has been accomplished over the last year.

Dr. Cassman: The National Institute of General Medical Sciences (NIGMS) established the Center in response to a growing need within NIGMS and NIH as a whole to address (a) the needs of the biological community with respect to the storage, retrieval and manipulation of biological data and (b) the use of these data to advance the newly emerging field of biological complexity. The first year has seen the rapid growth of the activities of this new Center. By the end of the year, the budget is expected to have grown to close to $40 million. Of this, only about one quarter results from the consolidation of activities already sponsored by NIGMS. The remainder represents new activities sponsored by the Center. These include biological complexity initiatives, an initiative to establish Centers of Excellence in Computational Biology as related to complex systems, a Biomath initiative undertaken jointly with the National Science Foundation as well as those applications received in response to the BISTI (Biomedical Information Science and Technology Initiative) initiatives assigned to NIGMS, and the newly established institutional predoctoral training program in Bioinformatics and Computational Biology. In addition, the Center has served as a focus within NIH for issues related to bioinformatics and computational biology. The Director of the Center serves as the chair of the NIH-wide BISTI consortium. This consortium is expected to announce initiatives by the end of the current fiscal year related to software development and the creation of NIH-wide Centers of Excellence in the area of Bioinformatics and Computational Biology.

BIOINFORMATICS

Mr. Regula: Does the research community have the capability and/or capacity to accept the vast amounts of data that is forthcoming?

Dr. Cassman: As the question implies, as it enters the 21st century, biology is rapidly becoming a data-rich discipline. The very complexity of biological systems presents unique challenges. For this very reason, the National Institute of General Medical Sciences (NIGMS) established the Center for Bioinformatics and Computational Biology to deal specifically with the development of computational

tools, including databases, to handle these data. In addition, several of our large initiatives, such as the protein structure initiative, the pharmocogenetics initiative, and the integrative and collaborative approaches to research initiative grants ("glue grants"), will generate large amounts of data that will be widely distributed to the broader scientific community. In each of these efforts, bioinformatics is a key component that receives major funding.

LEVEL OF SUPPORT FOR RESEARCH TRAINING

Mr. Regula: NIGMS supports 29 percent of all research trainees that receive assistance from NIH. Compared to the universe of research trainees, what percentage receive assistance from NIH?

Dr. Cassman: The NIGMS and NIH research training programs support young scientists at both the predoctoral and postdoctoral levels. At the predoctoral level, NIH provides support for about 25 – 30 % of the graduate students in biomedical sciences in U.S. universities and medical schools. These graduate students take part in organized programs and are supported by NIH training grants and fellowships during the early part of their training. Often, graduate students also receive some support during the latter stages of their predoctoral years when they may work on NIH or other funded research grants. Graduate students not supported by the NIH receive funds from other federal and state agencies, university fellowships and teaching assistantships, foundation awards, or use personal funds and loans.

With regard to those pursuing postdoctoral training, the NIH supports over 7,000 of these individuals, some on fellowships and some on training grants. Many others are supported as research assistants on NIH research grants. Funds from numerous other sources support a significantly larger number of individuals in postdoctoral positions in many different research settings. There is little reliable data on the biomedical postdoctoral training that takes place at institutions that do not grant graduate degrees.

OUTREACH TO SECONDARY SCHOOL STUDENTS

Mr. Regula: What does your Institute do to reach out to middle and high school students to peak their interest in biomedical research?

Dr. Cassman: NIGMS tries to encourage middle and high school students' interest in pursuing careers in biomedical research in two ways, primarily. First, most of the publications that NIGMS designs and produces are written at the middle and high school levels. This is done both to educate the American public at large about the important basic research efforts funded by NIGMS and to intrigue young people to learn more about these topics. The thrust of each edition of one of our publications, titled "Findings," is to present the work of two or three scientists in a way that conveys not only what exciting research topics they are pursuing, but also explains how they got interested in and then pursued a biomedical career. The second approach NIGMS takes

to piquing the interest of high school students in biomedical research is to support minority high school students who are seeking actual laboratory experiences. The Institute does this through supplements to ongoing research projects.

OTHER AREAS OF INFRASTRUCTURE

Mr. Regula: In addition to training, what other approaches do you use to address infrastructure needs?

Dr. Cassman: In addition to research training, the other infrastructure needs for which NIGMS provides support are primarily resources for performing basic biomedical research. These include programs for the development and use of state-of-the-art equipment, database development, and initiatives that develop large scale collaborative projects that result in significant resources being made available to the scientific community. One example is the initiative in structural genomics, which will generate a database of the three-dimensional structures of virtually all the proteins in nature. This post-genomic database will provide the basis for progress in many fields, including targeted drug design.

TREATMENT DEVELOPMENT PROGRAM

Mr. Regula: Tell me about NIMH's newly established treatment development program. What do you hope to accomplish through this program?

Dr. Nakamura: We believe NIMH can play an important role in accelerating the development of new and more effective medications to treat mental illness. Common and disabling mental illnesses such as schizophrenia have a range of symptoms, such as hallucinations, disorganized behavior, lack of motivation, poor social skills, and impaired thinking and problem solving. Currently available medications only target some of these symptoms. As a result, patients are often left with serious residual disabilities. For example, while one medication may be very effective in controlling hallucinations, it may do nothing to alleviate so-called negative symptoms such as lack of motivation. NIMH-funded basic research has yielded intriguing clues about biological and neurochemical processes that mediate different dimensions of mental illness symptoms. Our treatment development program will focus on translating these basic research findings into new and more effective treatments. Specifically, we will: a) collaborate with private industry in identifying new compounds to reduce particular symptoms that are inadequately treated by available medicines; b) develop better measures and methods to test the effectiveness of new medications against these symptoms; and c) work with academic, industry, and regulatory officials to achieve consensus about what dimensions of mental illness symptoms are inadequately remedied by available treatments and therefore represent important targets for new medication development. If regulatory agencies accept inadequately treated clinical symptoms as

valid endpoints for drug registration, the pharmaceutical industry will have a powerful economic incentive to focus drug development efforts on these important individual sources of disability.

CLINICAL RESEARCHER SHORTAGE

Mr. Regula: To what extent does the shortage of clinical researchers affect mental health research? What are you doing to address this problem?

Dr. Nakamura: Clinical researchers play many critical roles in the mental health research enterprise, ranging from conducting basic and disease-oriented research to serving as liaisons to patients and patient advocacy groups regarding the conduct and results of research. Patient-oriented researchers also play a critical role in the translation of basic research findings into clinically relevant research questions capable of elucidating the specific causes of mental disorders, ultimately leading to improved treatments and preventative interventions. A decline in the number of clinical researchers, particularly physicians, engaged in mental health research threatens our nation's ability to leverage advances in basic medical and behavioral science into treatments and eventually prevention of mental illness. The trend of fewer clinicians entering the research workforce is evident across all areas of medicine, but is especially problematic in psychiatry because of the decline in the number of graduate medical students who choose to train as psychiatrists. In 2001, only 3% of the total 16,000 U.S. medical graduates entered psychiatric residency training programs. This is a substantial decline from the historic high of 7-10% per year in the years following World War II which began to fall in the early 1970s.

There are several potential explanations for the decline in clinically trained individuals entering the mental health research arena. These include: substantial academic debt; the time required to prepare for a clinical research career; and the misperception that clinical researchers cannot compete successfully for funding with basic scientists. The inherent complexities of conducting patient-oriented research may serve as a deterrent as well. Issues associated with the decline of clinical researchers are complex, and will require comprehensive, long-term solutions involving NIH, academia, industry, and private foundations. Effective partnerships will also be important to sustain progress.

Ten percent of NIMH's current extramural budget supports training and career development opportunities for researchers. NIMH has undertaken numerous initiatives in collaboration with academia and professional organizations to address the shortfall of clinical researchers conducting mental health research, including: supporting the largest number of new Mentored Patient-Oriented Research Career Development awards of all NIH Institutes; initiating a new Mental Health Research Education Award designed to support clinical research education endeavors; and sponsoring an Institute of Medicine study to evaluate the impact of current psychiatric training requirements on the number of psychiatrists choosing to pursue careers in clinical research. NIMH is also

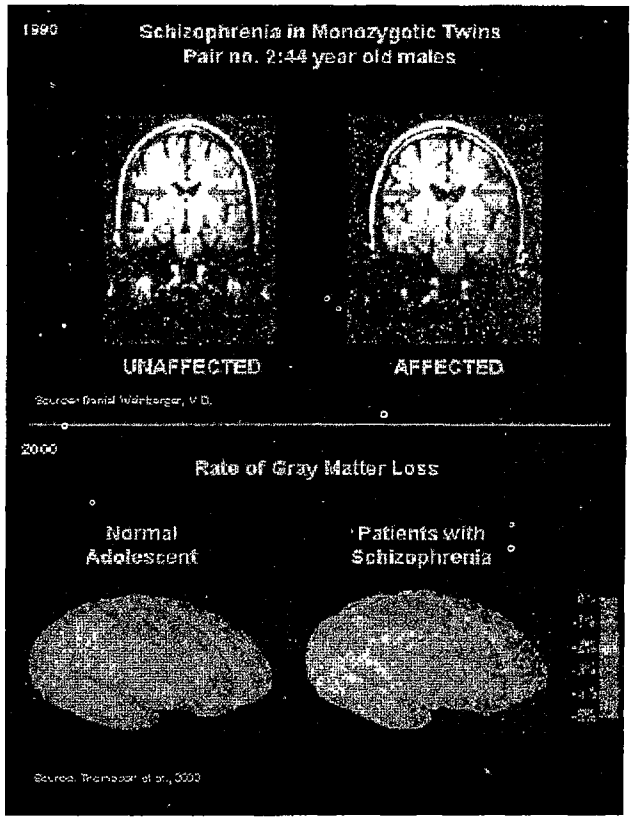
implementing the recently authorized loan repayment program for individuals who choose clinical research careers and plans to provide at least 25 repayment awards this year and to double that number next year.

PET SCANS

Mr. Regula: What are such tools such as PET scans telling us about the basic nature of mental disorders? Do you support research on the further development of such tools?

Dr. Nakamura: Noninvasive brain imaging approaches such as Positron Emission Tomography (PET) play an increasingly prominent role in efforts to understand the brain, its functions, behavior, and the neurobiology of mental illness. Researchers are using PET imaging to elucidate the brain circuits that regulate human cognition, anxiety, and emotion. For example, recent NIMH-supported studies using PET scanning (Shaw et al., 2002, Neuroimage 15: 661-674; Bremner et al., 1999, Biol. Psychiatry 45:806-816) have demonstrated that in patients with Post Traumatic Stress Disorder, the nature of the communication among a network of particular brain regions is different than that seen in subjects who do not have the disorder. This difference is thought to reflect the disruption of emotion, memory, and processing of visual information seen in these patients.

The image below provides a vivid illustration of the growing sophistication and utility of PET scanning and other brain imaging technologies. The two images on the top half of the illustration depict cross-sectional views of the brains of twins, one with schizophrenia, one without. The notable difference is the variation in ventricle size; that is, the butterfly-shaped "hole" in the center of the brain slice. Admittedly, the resolution of the image is weak and the PET scan could not clarify whether the difference in ventricle size was acutely associated with the illness, but this image constituted some of our earliest, tangible evidence that schizophrenia is a brain disorder. The images on the bottom half of the graphic were obtained just a year ago, by investigators using magnetic resonance imaging (MRI). In the study, the investigators scanned a group of teenagers at risk for early onset schizophrenia during a period of 5 years, and compared these scans with those taken of a group of healthy controls. In the patients, a pattern of gray matter loss began in a small region of the parietal cortex, where gray matter is lost normally in teens. Over the course of the study, however, the images revealed a virtual wildfire of tissue loss spreading across the brains of these teens as the schizophrenia progressed, with the extent of these structural changes reflecting the severity and time-course of patients' symptoms, including hallucinations and depression. These studies provide valuable insight into the differences in the brains of children with schizophrenia and other psychotic disorders as compared to normal children. Identifying these changes and their causes will help researchers to understand the mechanisms of psychotic disorders and, in the long run, develop more effective treatments.



PET instruments detect radioactive signals generated by probes (typically radioactive molecules that bind to particular proteins). The first available PET probes were designed to measure cerebral blood flow and metabolism of glucose in brain. Using these probes, researchers have identified regional changes in brain activity that correlate with the severity of clinical symptoms in depression and schizophrenia. PET measures of glucose metabolism are useful windows into the brain in studies to assess mood regulation in depression and sensory processing of information in schizophrenia. In drug treatment studies, PET imaging is a tool to assess drug effects on brain metabolism and to predict drug responses. There is an emerging interest in molecular imaging in medication development efforts. Using newly identified radioligands—radioactive molecules that bind to the same receptors that medications

do—researchers are using PET scanning to determine how therapeutic medications work. Researchers are beginning to use PET radioligands in clinical trials to assess disease severity and to monitor the progress of treatment. The use of PET imaging probes in clinical trials research holds the promise of identifying quantifiable markers that can be used to evaluate the efficacy of novel medications and predict clinical response or adverse effects.

NIMH supports the development of novel probes for PET imaging. The NIMH Intramural Research Program has established a new laboratory for development, evaluation, and implementation of PET tracers of relevance to neuropsychiatric disorders. In addition, NIMH, along with three other NIH institutes, solicited applications for grants to develop novel probes for use in functional neuroimaging studies using PET and Single Photon Emission Computed Tomography (SPECT). The overall goal of these initiatives is to accelerate the development of new probes for human studies and make them widely available to the research community.

APPLICATIONS FROM NEW INVESTIGATORS

Mr. Regula: The budget states that NIDCD is giving high priority to applications from new independent research scientists. Could you tell me more about whom these scientists might be and what you hope to accomplish?

Dr. Battey: New investigators are defined by the NIDCD as an investigator within 10 years of their terminal M.D., Ph.D. (or an equivalent) degree who has not yet successfully competed for and received an investigator initiated research grant from NIH. The 1997 NIH Report on New Investigators reported that the entry rate for new investigators into the ranks of NIH-supported investigators was only 9%. The NIDCD has developed a number of strategies to increase this entry rate above 9% and to more effectively counterbalance the loss of retiring senior investigators.

Across NIH, the initial peer review of applications from new investigators takes into consideration their more junior stature. Within NIDCD, new investigators that have marginally missed the NIDCD's funding payline are individually contacted by staff and encouraged to submit a letter to the NIDCD Advisory Council in which they respond to criticisms raised in the merit review of their grant application. Those 'New Investigator Letters' are individually reviewed at the Advisory Council meeting and may lead to special consideration and funding of the grant award, thus allowing a new investigator to expeditiously amend/clarify their application without formal resubmission.

NIDCD has also initiated steps designed to increase the pool of new investigators. NIDCD recently added an individual predoctoral fellowship program so that we now support young investigators at the predoctoral and postdoctoral levels. In recognition of the short and critical time period spent in such fellowship phases, the NIDCD has designed and implemented a process that compresses the receipt-to-funding time frame for fellowships to just four months. The benefits are that successful

applicants can get their research fellowship funding as quickly as four months. Unsuccessful applicants receive written reviews containing criticisms of their applications in approximately 12 - 14 weeks, allowing them the time to amend their application and submit for the very next fellowship receipt deadline. Consequently, both successful and unsuccessful fellowship applicants benefit from the unique expedited review and award process at NIDCD, allowing them to spend more of their crucial training time doing research, not waiting to hear if their application was successful or not.

SUPPORT OF PROMISING RESEARCH SCIENTISTS

Mr. Regula: What programs do you have to encourage new scientists to pursue careers in communication sciences and its disorders?

Dr. Battey: The NIDCD is highly committed to: 1) identifying and supporting those individuals who have the potential to develop into successful scientists in research on human communication in its normal and disordered states; and 2) facilitating the transition of such individuals from the training stage to the independent investigator career stage. Several programs have been implemented and recently augmented in pursuit of these goals.

The NIDCD has recently launched an individual fellowship program to support the dissertation research of promising doctoral candidates in the sciences of human communication. This program augments the Institute's active participation in the trans-NIH predoctoral fellowship programs for minority students and students with disabilities and the research supplement programs (the latter applicable to individuals across a broad career range) serving these two underrepresented groups. The NIDCD is one of very few NIH Institutes peer reviewing its pre- and postdoctoral fellowship applications based on an expedited submission-to-award schedule.

The NIDCD is particularly committed to fostering the development of highly promising clinician-scientists capable of "translating" basic research findings to the patient's bedside. We have initiated a special fellowship program to support MD/PhD candidates whose goal is to become physician-scientists in the sciences of human communication. We have augmented our mentored clinician-investigator career development awards to provide an enhanced level of salary support necessary to attract promising candidates from the surgical subspecialty areas to research. We have fashioned the NIDCD Small Grant (R03) program to assist both clinician-investigators and basic investigators transition to research independence. Approximately 50% of NIDCD R03 grant holders have been successful in winning a subsequent investigator-initiated R01 grant, the mainstay of NIH-supported research. The NIDCD has special provisions for newly-independent investigators submitting their first R01 grant application. Of the funds set aside each Advisory Council round for the award of meritorious research grant applications scoring below the automatic funding payline, half is set aside for new investigators. These new investigator applicants are also invited

to submit letter responding to critiques of their grant applications. These letters are considered by the NIDCD Advisory Council in its second-level review of grant applications.

TYPES OF EXTRAMURAL RESEARCH ADMINISTRATORS

Mr. Regula: What is a research administrator? Is this something that all Institutes should have?

Dr. Battey: NIDCD, like all NIH institutes and centers, has several types of extramural research administrators, i.e., administrative personnel whose work involves research grants and awards made to universities and other non-NIH entities such as hospitals and private research institutions (both public and for-profit).

Health Scientist Administrators plan and oversee research and research training in specific medical and scientific areas. Their duties include assisting extramural scientists in universities and other institutions with their interactions with NIH, analyzing the NIH's portfolio of ongoing research in their own areas, identifying specific scientific problems for which more research is needed, and developing strategies to stimulate research in those problems. Once grants are funded, Health Scientist Administrators review scientific progress based on annual progress reports and publications.

Scientific Review Administrators organize and oversee the process of peer review of grant applications. They convene groups of extramural scientists who read and critique the applications submitted by other extramural scientists. They must ensure that the reviewers are not only expert in their fields, but also fair, discreet, and free of conflicts of interest with respect to the applications being reviewed.

Grants Management Specialists actually obligate the federal funds that go to the universities and other extramural institutions in support of the research proposed in the grant applications. They work with the extramural institution's administrators to ensure that budgets are appropriate and that both institutions and investigators comply with regulations that apply to federal grant programs.

COCHLEAR IMPLANTS

Mr. Regula: What role did NIH play in the development of cochlear implant technology and what impact has this technology had on the welfare of babies with profound hearing loss?

Dr. Battey: The cochlear implant is the only sensory neural prosthesis in widespread clinical use. This device converts sound into electrical impulses on an array of electrodes surgically inserted into the inner ear, bypassing the damaged outer hair cells and stimulating the auditory nerve directly to restore the perception of sound to

individuals who are totally, or almost totally deaf. The NIH has played a significant and important role in sponsoring the development of cochlear implant technology. Two institutes have been particularly important in this development: the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Deafness and Other Communication Disorders (NIDCD). Cochlear implant research in the U.S. significantly increased with the establishment of the NIH Neural Prosthesis Program (NPP) in 1970. Over the past three decades, NIH support of the NPP and funding of extramural research activities to universities has established cochlear implant programs in the U.S. In addition, NIH support is providing a forum for scientists to share information through NIH-sponsored conferences and workshops. Advances in cochlear implant technology eventually resulted in the development of Food and Drug Administration regulations ensuring pre-market approval for safety and effectiveness of cochlear implants. With over thirty years of NIH research support, the cochlear implant has evolved from an experimental prosthesis to a miniature hearing device that is commercially available to assist those who are profoundly deaf or severely hearing impaired. Over 70,000 individuals have received cochlear implants worldwide.

Approximately 21,000 Americans have received cochlear implants, with about one-half of the recipients being children. NIH-supported research has been instrumental in showing the appropriateness of cochlear implants in infants with profound hearing impairment, the age when children could safely be implanted, and the importance of early intervention for language development. One of the anticipated benefits of implantation in children is improved acquisition of spoken language. Recent data indicate that the improvements in speech perception and language production shown in deaf children with cochlear implants have also resulted in better language and reading performance. With many states screening newborn infants for hearing impairment before discharge from the hospital, many more infants with hearing impairment will be identified at an early age when appropriate intervention, such as a cochlear implant, can be started that will optimize their long-term speech and language skills.

COCHLEAR IMPLANTS

Mr. Regula: What research is currently being conducted in this area?

Dr. Battey: It is likely that more infants will be identified with a hearing impairment, as newborn hearing screening becomes universal in the U.S. The cochlear implant is one treatment option available for these children, and clinicians are faced with the important issue of refining the criteria for cochlear implantation at a younger age. In an NIDCD-supported project, scientists are developing a reliable evaluation strategy, including accurate assessment of auditory thresholds to determine if a child is a candidate for a cochlear implant by 12 months of age.

NIDCD continues to conduct and support research to improve the performance of cochlear implants for all individuals who are severely hearing impaired. Research includes: development of better speech stimulation strategies, electrode design,

evaluation measures, fitting/programing strategies, understanding how the cochlear implant stimulates the auditory nerve, and improved performance in a noisy environment. Scientists are also developing cochlear implants with shorter electrodes for individuals with lesser degrees of hearing impairment who do not benefit from using a hearing aid. The benefit of binaural (both ears) implants is also being explored.

CLINICAL TRIALS NETWORK

Mr. Regula: NIDA established a clinical trials network in 1999 with the goal of moving treatment research into practice. How effective this network has been?

Dr. Hanson: This network has been extremely effective in moving treatment research into practice. It fosters researcher-practitioner bi-directional communication to conduct clinical trials on science-based drug abuse treatments. The CTN is a cooperative undertaking of NIDA, university drug abuse scientists, and community treatment providers in which researchers and practitioners work together to test research-based treatments in community settings. More than 90 Community Treatment Programs (CTPs) are involved in this national endeavor. The full involvement of both scientists and practitioners in all aspects of the CTN's work is now its hallmark. For example, treatment protocols to be run in the CTN must both retain the science base of new treatments but also ensure they are applicable in the clinic. Currently 19 science-based concepts are being developed into treatment protocols. These concepts include pharmacological, behavioral, and integrated behavioral and pharmacological approaches for treatment of a diverse population of drug dependent patients. Six of the research concepts are being implemented in over 50 CTPs in 15 States and the District of Columbia. As a result of the partnering between researchers and practitioners, we expect that when a CTN study demonstrates that a research-based therapy works in the clinic, the protocol for that treatment will be more quickly adopted as a standard of care by CTPs. Likewise, we anticipate that researchers will take the knowledge gained from working with practitioners back to their clinical settings to inform the design of new treatment studies that meet the real-world needs of the clinic. The establishment of agreed upon working protocols is just one of the examples of how the CTN is moving research into practice.

Mr. Regula: How many other Institutes have established similar networks? Do you think more networks should be established?

Dr. Hanson: At NIH, many Institutes have established clinical trials networks to conduct large-scale multi-site clinical trials. The following examples are provided to illustrate the different types of network currently supported by the NIH. NIDA's National Drug Abuse treatment Clinical Trial Network (CTN) is modeled after the NCI's Community Cooperative Oncology Program (CCOP). It also shares similarity with NIAID's The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). In addition, NIAID also supports the HIV Vaccine Trials Network (HVTN) in the United States and abroad and it is dedicated to the development of an HIV vaccine

through testing and evaluating candidate vaccines in clinical trials. The network includes 18 sites in the United States and 11 international sites, including sites in Africa, Asia, South America, and the Caribbean. The HVTN's global capacity will allow for rapid expansion as more vaccine candidates enter the pipeline for testing and development, and for carrying out larger scale studies of suitable vaccines.

In an effort to reduce the worldwide spread of HIV, NIH created the HIV Prevention Trials Network (HPTN), a global network of clinical trial sites that explores non-vaccine prevention strategies to reduce HIV transmission. The HPTN has nine sites in the United States and 16 sites overseas in Africa, Asia, Europe and South America. The network develops and evaluates both biomedical and behavioral intervention programs. Because HIV is transmitted via different routes in different populations, developing a variety of HIV prevention strategies will have a significant impact on reducing transmission rates and slowing the spread of HIV worldwide.

Another example is the NICHD Neonatal Research Network, an innovative multi-center collaborative research network that was established in 1986 to provide a format for the conduct of large, multi-center (16 centers) studies and trials to improve the care and outcome of sick infants. The Network has addressed the major problem areas in neonatal medicine with a number of landmark randomized controlled trials, observational studies, and outcomes research in the prevention and treatment of infection, chronic lung disease, brain injury, respiratory failure, eye disease of prematurity, birth asphyxia, and nutrition. The Network has led a number of collaborative international trials and trials funded jointly by other federal agencies and industry. The Neonatal Network is both productive and cost-effective. It has completed 15 large randomized trials and 15 large studies; it is currently conducting 5 randomized trials and 4 observational studies at an annual cost for the 16 Clinical Centers in FY02 of $5.2 million. Finally, Network research has changed medical practice – inhaled nitric oxide was approved by the FDA for use in infants for respiratory failure, obstetrical use of antenatal glucocorticoid therapy for mothers at risk for delivery of a preterm infant has increased from 18% to 80%, and a number of ineffective therapies have been discarded.

The NIH supports a diverse portfolio of clinical trials, ranging from small-scale, single-site studies of a few patients to large-scale, multi-site studies of hundreds and thousands of patients. In considering the optimal mechanism to support clinical trials, Institutes and Centers (IC's) consider a number of factors, including the nature and complexity of the trials. IC's would consider establishing more networks if the trial complexity warrants such mechanism. It is clear that networks create a critical mass of scientific and administrative expertise and infrastructure that substantially reduces the time and effort required to begin and manage clinical trials. However, the infrastructure and management challenges for small-scale, single-site studies would not warrant a network mechanism.

NATIONAL DRUG ABUSE TREATMENT CLINICAL TRIALS NETWORK (CTN) AND THE PRIVATE SECTOR

Mr. Regula: It's stated in the justification that NIDA is interested in involving the private sector in these network activities. Could you tell me more about this? What role do you see for the private sector

Dr. Hanson: NIDA has had a number of successful ventures with the private sector, such as our work with the Robert Wood Johnson Foundation in supporting research and dissemination endeavors that relate to tobacco and our work with some small pharmaceutical companies to help bring anti-addiction medications to fruition. NIDA would like to involve the private sector even more in NIDA activities; we see opportunities at a variety of levels, especially for NIDA's new treatment infrastructure, the National Drug Abuse Treatment Clinical Trials Network.

We would like to recruit more physicians, including psychiatrists and primary care doctors, and psychologists who work in private practice to become more involved in the network. We are also trying to expand the network to include private programs. The community-based treatment programs currently involved in the CTN are mostly publicly funded through their state block grants. A few, such as the Betty Ford Center in Rancho Mirage, California and the Caron Foundation in rural Pennsylvania, are privately funded. NIDA is interested in expanding the network to include additional private programs. This expansion would offer a different patient population as well as different practitioners the opportunity to be exposed and benefit from science-based treatments. Thirdly, NIDA is encouraging the involvement of private non-profit organizations, such as the Robert Wood Johnson Foundation, to assist in expanding sponsorship of dissemination activities to broader treatment communities after effective therapies are identified and packaged for dissemination.

INNOVATIVE MECHANISMS

Mr. Regula: Tell me about the new mechanisms NIDA is using to foster innovative research and research opportunities for new investigators.

Dr. Hanson: NIDA is employing a number of new mechanisms to foster innovative research and research opportunities for new investigators that will more rapidly advance our understanding of drug abuse and addiction. NIDA's "Cutting Edge Basis Research Awards (CEBRA)" will allow NIDA to fund research that is high risk and potentially high-impact and that is underrepresented or not included in NIDA's current portfolio. NIDA's "I-START: Rapid Funding for New Investigators in Brain Imaging" will stimulate growth in the cutting edge field of neuroimaging, NIDA plans to create a new award mechanism to more rapidly fund new investigators who want to work in the neuroimaging arena. I-START, like its model predecessor the Behavioral

Science Track Award for Rapid Transition B-START program, can expedite the entry of newly independent investigators into the drug addiction research field by offering small 1-year grants.

SHARED RESEARCH TOOLS

Mr. Regula: The goal of NCRR is to keep pace with changing investigator needs for research infrastructure, and to ensure that the biomedical community has ready access to enabling tools and technologies. Are you meeting this goal?

Dr. Vaitukaitis: Based on both the FASEB and NSF surveys, and from the large number of applications received for funding by the NCRR, infrastructure programs supporting purchase of instrumentation and access to complex, very expensive hardware and software at resource centers is meeting much of the goal of providing ready access to enabling tools and technologies for the biomedical research community.

SHARED RESEARCH TOOLS

Mr. Regula: How do you determine whether you are meeting these goals? What evaluations or measurements do you have to guide you?

Dr. Vaitukaitis: In October of 1999, the Federation of American Societies for Experimental Biology (FASEB) carried out a survey of NIH supported investigators to determine if current programs were meeting the researchers' needs for major equipment. The results of the survey showed that the NCRR instrumentation programs were critical to meeting the need for major instrumentation required for scientific progress, and recommended increasing the level of support. The recent FASEB policy paper on Federal Funding for Biomedical and Related Life Sciences Research reinforced the need for a continued emphasis on funding instrumentation. The most recent NSF study "2001 Scientific and Engineering Research Facilities" survey data also showed that biological and medical science programs remain most in need of additional space including single pieces of non-fixed equipment costing at least $1 million, supporting the initiation of the NCRR program for funding high-end equipment costing over $750,000.

Mr. Regula: The tools and technology researchers need are expensive and scarce. What programs do you have to get these tools into the hands of researchers?

Dr. Vaitukaitis: NCRR (1) makes awards for purchase of expensive, high technology instrumentation needed for advanced biomedical research, (2) supports resources and scientists who provide expertise to help investigators address complex scientific queries through modifying existing or developing new state-of-the-art instrumentation, and (3) provides access to advanced technologies via the Internet, or through virtual laboratories; permit access to the latest in biomedical technology by researchers not located at one of the major research centers.

The NCRR Shared Instrumentation Grant Program (SIG) allows NIH investigators to obtain equipment that would be too expensive to purchase with research project grant funding. The cost range for the instruments is between $100,000 and $500,000 and the instrument must be shared by at least three NIH grantees. This program has been in effect for a number of years.

In FY 2002, NCRR assessed the need for more expensive instrumentation and issued a request for applications (RFA) for single items of equipment costing over $750,000. The RFA drew an enthusiastic response from the community.

NCRR supports almost 70 research resources across the country that provide access and training for researchers who require the most advanced instrumentation and software available. These resources include synchrotron light sources, proteomics centers, imaging centers, and software for modeling, analysis and display of complex biomedical data.

Access to advanced instrumentation and software has been significantly enhanced in the past few years by working in partnership and building upon the NSF investment in the Internet and grid computation for sharing these resources and creating virtual laboratories via the worldwide web.

B&F INFRASTRUCTURE

Mr. Regula: What procedures are in place to decide the infrastructure needs of the agency?

Dr. Kirschstein: The annual Buildings and Facilities (B&F) budget request supports long-standing commitments to create, expand, and sustain a robust, modern, safe and secure physical infrastructure for the conduct of basic and clinical research. With the intent to inject more accountability, decrease duplication, and integrate a coordinated strategic planning and priority setting process across HHS facilities, the FY 2003 Budget establishes a new HHS Health Facilities Construction and Management Fund that will fund HHS construction projects within the Office of the Secretary. HHS will provide the oversight and management of all construction projects from a centralized office in the Office of the Secretary. By centralizing the financial management of construction projects and continuously monitoring the progress being made in relationship to the dollars being spent, more accountability and efficiency will be brought into the construction process.

SAFETY MASTER PLAN

Mr. Regula: NIH has conducted a comprehensive safety survey and developed a master plan for safety improvements at NIH. What is the status of implementation of this plan? Do you have adequate resources to complete the plan on time?

Dr. Kirschstein: In 1993, NIH developed the NIH Fire Protection Master Plan to provide safety improvements in both fire protection systems and in individual NIH facilities. The Fire Protection Master Plan was based on a comprehensive survey of NIH facilities conducted by both NIH fire prevention inspectors and fire protection consultants.

With funds received to date, NIH has executed the top priority elements within the master plan. These projects include: the installation of an improved fire detection, alarm, and reporting system within the NIH Clinical Center; an upgrade of the automatic fire detection and suppression systems in a number of NIH's older laboratories and administrative facilities; and the correction of a number of identified life safety projects.

The NIH is carrying out a systematic approach for updating and funding the Fire Protection Master Plan. Annually, the NIH re-prioritizes the elements of the master plan to identify an annual list of projects to be executed within the available funds. This re-prioritization is based upon the risk to people and property, changing research focus and methods, building technology, best practices, life safety and environmental control regulations, the actual condition of the facilities, and progress made in correcting the deficiencies through this program, as well as other renovation projects. Additional resources are needed to complete components of the 1993 Master Plan including the campus-wide fire alarm reporting system; installation of automatic fire detection and suppression systems in the remaining NIH older campus facilities; the automatic fire detection and suppression systems at the NIH Animal Center including a new water storage tank for fire protection; and new initiatives to address additional fire and life safety projects encountered during alterations of facilities that support the NIH research mission.

Mr. Regula: Provide a copy of the plan for the record.

Dr. Kirschstein: A copy of the 1993 master plan will be provided separately for the record.

PHYSICAL SECURITY

Mr. Regula: Why hasn't there been a request for physical security improvements prior to September 11, 2001?

Dr. Kirschstein: The NIH has always recognized the need for a comprehensive security program that addresses the NIH physical plant, new technology and operational procedures. Prior to September 11, NIH's security program was mainly focused on operational and technology improvements and there was little in the way of perimeter and building entry security. Acting first on a security assessment conducted in accordance with Department of Justice standards, as well as a subsequent security study requested by Congress, the NIH has increased resources to enhance security. These

improvements were built into ongoing Buildings and Facilities (B&F) projects, and funds from centrally furnished services were used primarily to improve emergency communications, guard services and some physical security upgrades.

Since September 11, there has been a focused effort to ensure that all Federal facilities are secured from the increased threat of potential terrorist and criminal activity. NIH implemented heightened security procedures to reduce the risk of potential harm to people and property in all of its facilities in compliance with Department of Justice standards, General Services Administration guidelines, and DHHS directives. In response to an IG report presented to the NIH on security of NIH laboratories, NIH developed a comprehensive plan of physical security improvements. The proposed improvements are aimed at providing a perimeter security system, infrastructure for effective emergency response, enhancements to the information technology capacities and capabilities, and upgrades to specific laboratories and buildings. The construction of the physical security improvements is a prerequisite to ensuring a safe and secure environment on the NIH sites in the most cost-effective and efficient manner, with the least imposition on the people involved, both patients and employees and the mission of the NIH.

PHYSICAL SECURITY IMPROVEMENTS

Mr. Regula: Provide a detailed breakout of the $80 million requested for physical security improvements.

Dr. Kirschstein: The proposed improvements are the second and largest increment of the physical security plan that NIH is implementing as part of a comprehensive security program aimed at providing a safe and secure environment for the conduct of its mission. The plan follows a system of concentric levels of security from the outermost areas of the site and works inward, toward individual buildings and areas within buildings. The first element of the security plan, a perimeter fence around the Bethesda campus, is being provided through FY 2002 funding. The FY 2003 request for $80 million completes the perimeter security system, provides necessary infrastructure upgrades and addresses sensitive building areas.

The request comprises the following projects:

- a Visitor Center for welcoming and screening visitors and vehicles, issuing visitor passes and providing central campus-wide transportation services;
- a Delivery Clearance Center for managing and screening deliveries of scientific and other equipment and materials to the campus;
- an internal Campus Loop Road for effective emergency response and efficient circulation of a large number of commercial and employee vehicles;

- enhancements to the information technology infrastructure to increase capacity of communications systems, minimize network security breaches and provide backup capabilities;

- enhancements to specific laboratories and facilities to make building envelopes more resistant to the effects of hostile actions and upgrade electronic building security systems; and

- a similar range of security projects at a smaller scale for the Rocky Mountain Laboratory, an NIH facility of the National Institute of Allergy and Infectious Diseases at Hamilton, Montana.

These improvements are consistent with direction given by the Executive Branch (Department of Justice, Office of Homeland Security, et.al.) and the Department of Health and Human Services (HHS), "best practices," and a report written by the HHS Inspector General. Together with enhanced technology systems and operational changes that NIH is implementing, the planned projects will bolster our ability to prevent, detect and respond to a variety of security risks, and will enable NIH to effectively address a range of federal "alerts levels" as necessary.

REPAIRS AND IMPROVEMENTS

Mr. Regula: Provide a breakout of the $56.6 million requested for repairs and improvements.

Dr. Kirschstein: For FY 2003 the $56.5 million requested for repair and improvements will fund the following projects:

Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Accrediation projects – $2.1 Million: These projects are necessary to maintain operation of the Clinical Center and to comply with the hospital accreditation requirements and include: repair of HVAC systems, electrical systems, fire doors/walls, emergency power, distilled water, domestic water and sewer, and medical gas, compressed air and natural gas distribution systems in the Clinical Center and ACRF .

Campus-wide Utility Distribution Systems – $18.4 Million: Projects to be addressed include repair, replacement, or upgrade of the primary campus (exterior) distribution systems and associated equipment for high voltage electricity, domestic water, sewer, natural gas, chilled water, and emergency power.

Interior Utility Systems – $6.5 Million: Projects to be addressed include all repairs/upgrades to the utility systems within the building. This consists of the plumbing systems, electrical systems, lighting systems, domestic water systems, sewer system, compressed air systems, and HVAC systems.

Structural Repairs – $4.2 Million: Projects to be addressed include the repair of the structural support/decking of the existing parking structures on the NIH campus, all roof repairs and replacement, all structural member repairs, foundation repairs, and all ground water infiltration repairs.

Public Areas Upgrades – $3.2 Million: Projects to be addressed include the repair and upgrade of all public areas including corridors, public restrooms, and support areas.

Physical Plant Security Upgrades – $6.1 Million: Projects to be addressed include the repair and upgrade of the building access security system, for both internal and external entrances.

Support for Off-campus NIH Facilities – $5.9 Million: Projects to be addressed include the major replacement and upgrading of HVAC, electrical, and other utility systems at off campus locations. These include the National Institute of Environmental Health Sciences (NIEHS) in North Carolina, the Frederick Cancer Research and Development Center (FCRDC) in Frederick, Maryland, Gerontology Research Center (GRC) in Baltimore, and the Rocky Mountain Laboratory in Hamilton, Montana.

Emergency Minor Repairs – $2.2 Million: Projects to be addressed include all emergency and minor repairs (less than $25,000) to the building plumbing systems, electrical systems, lighting systems, domestic water systems, sewer system, compressed air systems, HVAC systems, laboratory hood ventilation.

Building 10 Repair – $6.2 Million: Projects to be addressed include the east utility tunnel construction, upgrade of high voltage electrical cables and vaults, upgrade of HVAC and other mechanical systems to support changing requirements to support ongoing research.

Roads and other site work – $1.7 Million: Projects to be addressed include the repair or replacement of all roads, sidewalks, parking lots, retaining walls, street and directional signage, storm drainage systems, and street lighting.

REPAIR AND IMPROVEMENT PROJECTS

Mr. Regula: Provide a list of the backlog repair and improvement projects including cost of the project.

Dr. Kirschstein: The NIH Repairs and Improvement (R&I) program supports major repairs, preventive maintenance and improvements to the physical plants, including grounds and facilities for which NIH has the property-holding responsibility. The goal of the R&I program is to sustain efficient and effective facility performance throughout the life cycle of the facility to meet NIH's ongoing research mission. While some of these projects are one-time projects, many are cyclical and predictable, and are planned for. The FY 2003 Budget supports the R&I goal by requesting a total of

$56.5 million for planned projects, including the enhancement of utility tunnels, repair major roof, upgrade building automation systems, repair parking facilities, upgrade physical plant security, repair and upgrade heating, ventilation air conditioning, and electrical systems.

ESSENTIAL SAFETY AND REGULATORY COMPLIANCE PROGRAMS

Mr. Regula: Provide a list of the backlog safety and regulatory compliance projects including cost of the project.

Dr. Kirschstein: The FY 2003 Budget requests $6 million for safety and regulatory compliance projects. Planned projects to be addressed in FY 2003 include asbestos abatement, fire protection and life safety, indoor air quality improvement, structural modifications to accommodate persons with disabilities, and animal research facilities rehabilitation.

BIOSAFETY LEVEL 4 LABS

Mr. Regula: The Biosafety Level 4 lab at the Rocky Mountain site cost $66.5 million whereas the one at Ft. Detrick is projected to cost $105 million. What is the difference in cost?

Dr. Kirschstein: The main reason why there is a cost difference between the two facilities is because they are of different sizes. The facility at the Rocky Mountain site is approximately 30,000 gross square feet, and the facility at Ft. Detrick is approximately 100,000 gross square feet. The size of the two facilities is driven by programmatic differences. The facility at the Rocky Mountain site contains primarily Biosafety Level 4 (BSL-4) labs and support space, while the facility at Ft. Detrick contains clinical space, in addition to BSL-4 labs, and support space. While size significantly influences the cost differential between the two projects, there are other factors that influence cost such as functional composition and geographic location.

LABORATORY AT FT. DETRICK

Mr. Regula: The lab at Ft. Detrick will allow for collaborations with the Army. Why isn't the Army contributing to the construction of this lab?

Dr. Fauci: Lack of specialized, high-containment labs, like the one proposed for Ft. Detrick, is the most critical factor that limits research on the most dangerous and highly-infectious pathogens. The Army currently has a BSL-4 lab on Ft. Detrick – it is one of only three operating BSL-4 labs in the nation.

The NIH lab to be built on Ft. Detrick is to address NIH's mission-critical research, which differ significantly from the requirements of the U.S. military. Protecting the civilian population requires a much broader range of research and the NIH lab will support research for all segments of the civilian population, including the

elderly, children, infants, and people with suppressed immune systems caused by disease, therapeutic drugs or other reasons. Building this lab at Ft. Detrick, as compared to building it elsewhere, brings two distinctive advantages – it will facilitate cross-transfer of scientific knowledge and expertise between the scientific staff at NIH and the Army because of the co-location of the two BSL-4 labs; and the physical security of the lab will be enhanced because the lab will be on a secured military installation.

CENTER FOR BIOTERRORISM AND EMERGING INFECTIONS

Mr. Regula: Does the $186.1 million requested for the Center for Bioterrorism and Emerging Infections include the cost of construction of a multi-level parking garage? If so, how much is for the Center and how much is for the parking garage?

Dr. Kirschstein: The construction of the Center for Bioterrorism and Emerging Infections on the proposed site will replace the surface lots currently located on the site.

The parking lots currently on this site provide almost 1,300 employee parking spaces. We are proposing that these spaces be replaced in a multi-level parking structure to replace sprawling surface lots, restore landscaping, improve management of storm water runoff and enhance the natural resources and environmental qualities of the campus and the region.

As NIH continues to respond to new biomedical research initiatives including bioterrorism research, we have experienced an unprecedented growth in our construction program, which has resulted in the elimination of almost 2,000 parking spaces on the campus over the past few years. While we have intensified our transportation management programs with impressive results in reducing vehicle trips to the campus and increasing use of public transportation, a parking loss of this magnitude could affect NIH's ability to recruit and retain staff.

Of the requested $186.1 million, $21.8 million is the cost of construction for a 1,250-car multi-level parking facility.

SEVERE MENTAL ILLNESS

Mr. Istook: Dr. Kirschstein, what efforts are underway at NIH and NIMH to focus greater attention and resources on promising research at the basic, clinical, and services levels on severe mental illness such as schizophrenia, bipolar disorder and major depression to ensure that advances rapidly translate into better treatment and service for individuals living with these illnesses? How much is specifically being spent on research specifically targeted to Traumatic Brain Injury?

Dr. Kirschstein: In keeping with the overall mission of NIH, all research supported by NIMH has relevance to an improved understanding of mental disorders; still, several major research thrusts now underway are directing unprecedented attention and resources to activities assigned to improve treatment and services for mental disorders both at the individual clinical and public health levels. The generation of knowledge that will lead to improved care for persons with mental disorders constitutes the core of the NIMH's scientific and public health mission, a mission that gained urgency with the conclusion of the WHO/World Bank/Harvard School of Public Health *Global Burden of Disease* study that mental disorders account for four out of the leading ten causes of disability worldwide, with depression the first-ranked cause of disability in economically developed nations. Accordingly, a key NIMH initiative is the preparation of a Research Strategic Plan for Mood Disorders, primarily major depression and bipolar disorder. Over the course of the past year, NIMH staff, working with 130 extramural/intramural scientists and public representatives, have analyzed the most current knowledge and research on mood disorders in ten broad areas of science, ranging from genetics to service delivery. The plan outlines the goals and implementation steps to be taken to advance our understanding of the brain, human behavior, and specific pathology involved in depression and bipolar disorder. The plan, which will serve as a prototype for future disorder-specific strategic planning efforts, will set goals for developing new treatments and enhancing access to appropriate and effective treatments.

The very structure – and thus the operational capabilities – of NIMH is geared to the broadest possible scientific coverage of clinically relevant research. Each of the Institute's three major extramural divisions assumes responsibility for research on mental illness, while the task of translational research – that is, applying knowledge gained at each level of analysis to clinical and service systems – is shared across NIMH. In practice, this means that the Division of Neuroscience and Basic Behavioral Science, which is the locus for strong molecular genetics and fundamental behavioral research, also administers an innovative program of translational research centers, wherein major universities receive support to foster collaboration among diverse disciplines and departments to examine a particular disorder, such as schizophrenia. In the Division of Services and Intervention Research, immediate treatment needs are being addressed through an unprecedented series of multi-year clinical effectiveness trials that focus on discrete clinical issues: adolescent depression, sequenced treatment for adult depression, the use of atypical anti-psychotic medications in schizophrenia and depression, and enhanced treatments for bipolar disorder. Yet another illustration of the Institute's

priority on improving clinical care is evident in a new Treatment Development Initiative that will foster collaboration among NIMH, the FDA, and the pharmaceutical industry with the aim of introducing fundamentally new approaches to the development of treatments for mental disorders. In the NIMH Intramural Research Program, a major new Mood and Anxiety Disorders research program has been established that has recruited senior investigators from academia and now stands at the leading edge of research aimed at understanding and measuring structural changes in the brain associated with depression, chronic stress, and post-traumatic stress disorder, and at developing brain-based biomarkers to be used in monitoring treatment progress and outcome. It is noteworthy, too, that NIMH has created a new program in dissemination of research to fund studies that seek to understand the best ways to ensure that quality services are provided to community populations.

In Fiscal Year 2001 NIMH spent $1,374,000 on Traumatic Brain Injury.

RESEARCH PRIORITIES AT NIMH

Mr. Istook: Dr. Nakamura, we know you are interested in reshaping research priorities within all of the NIH institutes (including NIMH) to better reflect public health needs. At NIMH, several recent Mental Health Advisory Council reports, have recommended improving the relevance of prevention research into early interventions, clinical research to actual practice, and of behavioral research to serious mental illnesses. Could you please discuss some of the difficulties you've encountered in continuing NIMH's efforts to insure research is done on the greatest public health needs?

Dr. Nakamura: NIMH has mounted many initiatives to speed the translation of basic research into treatment and prevention efforts for mental disorders and behavioral problems that present important public health burdens, such as schizophrenia, depression, borderline personality disorder, and youth antisocial behavior. While each area poses its own particular research challenges, certain issues at various steps of the translational process cut across those which NIH is working to address. For example, NIMH is supporting research to: 1) translate biological and behavioral risk factors into targeted interventions for exploratory studies; 2) provide more systematic testing of interventions identified in preliminary studies as promising for prevention or clinical practice; 3) benefit from better linkage to other agencies for large-scale community trials of interventions of proven worth in intermediate trials. In addition, intensive efforts are being supported to overcome several structural barriers that impede translational prevention research. These include: 1) fostering multidisciplinary research training to improve collaboration and communication across research fields, teams and departments; 2) encouraging the creation of multidisciplinary peer review panels that are receptive to new kinds of translational research; 3) providing incentives to academic institutions to promote essential long-term prevention studies, even though some studies may lag in producing publishable results. Finally, NIMH is increasing its efforts to disseminate well-established research findings to those who can best apply them to

clinical care and prevention. For example, in the area of youth antisocial behavior, a mature body of research information suggests a number of scientifically well-documented prevention approaches, but they are not yet well recognized or widely adopted. At the same time, other widespread prevention approaches have been demonstrated to be ineffective or harmful. NIMH is working to disseminate these research findings to multiple audiences, including: researchers, practitioners, federal and local policymakers, and law enforcement and justice personnel.

SUCCESS RATES

Mr. Istook: Where does NIMH stand relative to other NIH institutes on the rate of grants submitted and funded?

Dr. Nakamura: In FY 2001 the average success rate (awarded grants as a percentage of total grant applications) for research project grants was 32 percent NIH-wide. Success rates across the 23 NIH Institutes and Centers ranged from a high of 43 percent to a low of 17 percent. The NIMH ranked 14th from the highest with a success rate of 31 percent.

SCHIZOPHRENIA RESEARCH

Mr. Istook: Discuss the budget for the last 8 years on schizophrenia. Discuss advances in the field, if any, and promising areas of research.

Dr. Nakamura: The budget for schizophrenia research for the last eight years is as follows:

Total NIMH Spending for Schizophrenia	Total NIH Spending for Schizophrenia
FY 1994 Actual – $110,416,000	$113,147,000
FY 1995 Actual – $108,900,000	$112,016,000
FY 1996 Actual - $108,811,000	$111,479,000
FY 1997 Actual - $108,659,000	$110,868,000
FY 1998 Actual – $132,455,000	$135,356,000
FY 1999 Actual - $196,515,000	$200,562,000
FY 2000 Actual - $234,799,000	$240,966,000
FY 2001 Actual - $265,294,000	$276,068,000

We stand on the verge of a revolution in our understanding of schizophrenia and our ability to treat people who suffer from this devastating illness. Not so long ago, a diagnosis of schizophrenia was considered by many to be the psychiatric equivalent of a terminal illness. With the introduction, first of clozapine, then more recently, a whole series of "atypical" antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, and soon aripiprazole and iloperidone), entirely new vistas have opened in the pharmacotherapy of schizophrenia. A major National Institute of Mental Health

(NIMH) sponsored clinical trial (with sites in 34 different states) is comparing these new antipsychotics (Clinical Antipsychotic Trials of Intervention Effectiveness, CATIE), and will define how they should be used to treat schizophrenia. These new antipsychotics seem to allow patients, families, and their clinicians to focus on coping with illness, rather than just symptom control. It appears that, with appropriate pharmacotherapy and psychosocial rehabilitation, many people with schizophrenia may be able to lead productive, meaningful lives.

In addition in 2001, NIMH launched a 4-site 5-year clinical trial to study the effectiveness of 3 different antipsychotic medications for children and adolescents (8-19 year old) suffering from schizophrenia, schizophreniform disorder, or schizoaffective disorder. Both short- and long-term effects will be comprehensively assessed for up to 1 year of treatment. The study is conducted under a cooperative agreement at the University of North Carolina (Dr. Jeffrey Lieberman), University of Washington (Dr. Jon McClellan), Case Western University (Dr. Robert Findling), and Harvard University (Dr. Jean Frazier).

While illness management in schizophrenia is important, it is not a cure. Finding a cure will depend on understanding what has gone wrong in the brains of people with schizophrenia. Advances in basic neuroscience, and sequencing the human genome, as well as development of sophisticated neuroimaging techniques offer hope that the puzzle of schizophrenia will be solved. We have long known that schizophrenia can be inherited, but because multiple genes are involved, previous studies were too small to identify them. The NIMH has set out to gather a sufficiently large number of families with more than several members affected by schizophrenia to pin down the genes that predispose people to developing the illness. Once these are identified and with the new knowledge of the human genome, the function of certain genes in the brain can be learned and a whole new generation of specific treatments may become possible.

Through sophisticated new techniques to image brain function, we are increasingly able to understand the neural circuitry that underlies the symptoms of schizophrenia. With the development of methods to noninvasively stimulate selected regions of brain, it even may be possible to turn off some of the troubling hallucinations and delusions suffered by patients with schizophrenia.

Finally, over the past decade, it has become increasingly clear that schizophrenia can be a disorder of brain development. Some subtle alteration in neuronal migration or connectivity as the brain develops later may become expressed as schizophrenia. In other words, since the "abnormality" that causes schizophrenia may be present well before a person develops overt psychosis, something must happen to trigger onset of the illness. If this is the case, then it may be possible to identify young people at risk for psychosis before active symptoms disrupt social, academic and vocational functioning. NIMH is developing methods to identify individuals in the earliest stages of schizophrenia, trying to prevent chronic disability through early intervention, and hoping

that this will eventually lead to treatments that can actually prevent onset of illness. While this prospect is exciting, there are also many ethical dilemmas that must be confronted before any such attempts at primary prevention can be made.

While schizophrenia remains the most disabling of all mental disorders, over the last eight years, our ability to manage the illness and improve outcomes and our understanding of its basic biology have improved dramatically.

ACCESSING THE NEWEST ADVANCED TREATMENTS

Mr. Istook: In the last decade, many new treatments and services have been developed and proven for severe mental illnesses such as schizophrenia. What efforts are underway (or ongoing) to ensure that the improved treatment interventions being developed now will be effectively disseminated to providers? Is NIMH collaborating with SAMHSA and CMHS on these efforts?

Dr. Nakamura: The NIMH has a specific program in research on dissemination and implementation of new knowledge that supports grants to find ways to ensure that effective treatments are brought to community practice. Ongoing activities in this program include a new announcement calling for grant applications in this area; new funding mechanisms to promote this area (including one jointly issued with CMHS on Children's Services); and sponsorship of workshops and conferences to foster new research ideas in this area. An example is a recent research workshop focused on implementing evidence-based practices into the public mental health sector.

NIMH has collaborated with SAMHSA, especially CHMS, on issues related to improving the implementation of new treatment interventions. CMHS representatives were actively involved in recent workshops and discussions about joint funding of future projects. Other collaborative efforts are underway to foster new research opportunities and implementation strategies.

BASIC AND FUNDAMENTAL RESEARCH

Mrs. Northup: Without targeting your research toward specific diseases and disorders, how do you determine where basic and fundamental research needs to be conducted?

Dr. Cassman: NIGMS primarily relies on investigator-initiated research hypotheses to determine the appropriate directions for the basic and fundamental research that the Institute supports. Investigators ask for grant support in areas where they believe progress can be made on fundamental biological questions. Their ideas are then subjected to peer review, during which experts in the proposed field of study render judgments about the scientific merit of the proposed research projects. The Institute Advisory Council and the scientific staff of the Institute then make funding decisions based primarily on scientific merit, but also considering the potential impact of the research and the need to balance the research portfolio.

In addition, the Institute issues announcements requesting applications in areas targeted for additional research. These are generated after broad consultation with the scientific community and the NIGMS Advisory Council.

MEDICAL SCIENTIST TRAINING PROGRAM

Mrs. Northup: The Medical Scientist Training Program provides investigators who can bridge the gap between basic and clinical research. How are researchers selected for this program? How many participate? How do you recruit people?

Dr. Cassman: The Medical Scientist Training Program (MSTP) is institutionally-based. NIGMS funds programs at 39 medical schools with over 900 students on these grants. However, many more students participate in MSTP programs at any one time than are funded by NIGMS. Our best estimate is that for every student we fund, 2 other students are funded by other means. The medical schools themselves recruit and enroll the trainees. Typically, from thousands of applicants, the schools select candidates with outstanding undergraduate records and significant research experience. The students are selected for commitment to research, and their ability to thrive in a very demanding environment where they must be extremely focused, efficient, and hard-working.

PHARMACOGENETICS

Mrs. Northup: In Pharmacogenetics you are studying how genes affect the way people respond to medicine. Have you found any research on why some people go on to abuse a drug and others don't, or why some people become addicted and others do not? Are there any common indicators or symptoms that people can look for to know if they are predisposed?

Dr. Cassman: NIGMS-supported research conducted by the Pharmacogenetics Research Network is focused on understanding the differences among people based upon their genes. Variations in people's genes might eventually explain how they respond differently to therapeutic medicines. At the present time, this research effort includes drugs used to treat heart disease, cancer, and depression. Right now it does not include drugs of abuse or abusive behavior, because that is the purview of the National Institute of Drug Abuse (NIDA), and that Institute is not participating in this research network. But some fundamental underlying systems (for example, the enzymes that are responsible for the conversion of drugs to new active compounds, or metabolites; or the transporters that are responsible for the uptake of drugs into the brain's "pleasure centers") will be understood better as a result of the Pharmacogenetics Research Network, and this will likely lay a foundation for research on drugs that affect addiction.

NIGMS also supports the PharmGKB knowledge base as part of the Pharmacogenetics Research Network. As valid clinical information is accumulated, such as is described in the question, it will be stored as a "clinical outcome" in the knowledge base. Significant research in this area is currently being supported by NIDA, and as results are learned, they can be deposited in PharmGKB, which is intended as an open resource for all investigators working in the pharmacogenetics area.

EARLY NEWBORN HEARING SCREENING

Mrs. Northup: Do we have any research on hearing that has come from the newborn hearing screening program?

Dr. Battey: The National Institute on Deafness and Other Communication Disorders (NIDCD) has been supporting research studying hearing impairment in newborn and infants. The NIDCD completed support of a five-year, multi-center study on neonatal hearing impairment and scientists continue to publish new findings in this area. For example, data from the study demonstrated that three methods commonly used in neonatal hearing screening, (auditory brainstem response (ABR), transient otoacoustic emissions (TEOAEs), and distortion product otoacoustic emissions (DPOAEs), work equally well, and that successful programs with low referral rates can be designed and implemented using any of the three methodologies. The study also showed that monitoring an infant's behavior to an auditory stimulus (a behavioral audiometry) can be done reliably for children at 8 to 12 months of age. In addition to advances in screening methodologies, the appropriate training of qualified personnel to conduct hearing screening is important to contributing to reliable test results.

Scientists supported by the NIDCD have examined the importance of age at enrollment in intervention programs and subsequent language outcomes for a group of deaf and hard-of-hearing children. Significantly better language scores were associated with early enrollment. Children enrolled before 11 months of age had stronger vocabulary and verbal reasoning skills at 5 years of age than did children enrolled at a later time. High levels of family involvement correlated with positive language

outcomes, and conversely, limited family involvement was associated with significant language delays at age 5, especially when intervention began later in childhood. These results provide further evidence that children will benefit when early identification of hearing loss is combined with an early intervention strategy that actively involves family participation.

Measures are currently available which can identify children whose speech and language will be notably delayed or impaired early in development. The NIDCD is supporting clinical studies/trials to: (1) determine and validate outcome measures to evaluate intervention strategies employed in children at all ages; (2) develop new intervention strategies, and determine which strategies are optimal for a given individual in their environment; (3) identify the early, sensitive periods for acquisition of speech and language in infants with greater precision; and (4) introduce these intervention strategies into the clinical practice of physicians, audiologists, and speech-language pathologists.

With the availability of new screening methods, not only will infants with severe hearing impairment be identified much earlier in life but infants with lesser degrees of hearing impairment are now also being identified. Advances in the genetics of hereditary hearing impairment and in the early identification of hearing impairment have now converged. These advances have led some to suggest genetic testing/evaluation for all infants who are identified with a hearing loss at birth. In consideration of these developments, the NIDCD and the National Human Genome Research Institute, (NHGRI), are collaborating on an initiative to address the clinical relationship between genetic and audiologic/otologic information, as well as to address the clinical validity and utility of genetic testing in the diagnosis, treatment and management of hearing impairment.

NIDCD-supported scientists are also examining means to close the gaps between identification of hearing loss in infants and the provision of appropriate interventions. Historically, there have been delays between identifying hearing loss in infants and referral for intervention. In order to optimize the benefits of early detection, the scientists have developed programs to educate medical professionals, early interventionists, and parents about newborn hearing screening and the availability and benefits of intervention strategies for language development. In addition, NIDCD supported researchers are including infants that were identified in State early newborn screening programs as participants in further research studies of hearing impairment.

SPEECH DEVELOPMENT IN CHILDREN WITH HEARING LOSS

Mrs. Northup: As you know, auditory stimulation is an important component in developing learning skills related to reading. What has your research shown about how to intervene to ensure that hearing problems don't turn into learning problems?

Dr. Battey: NIDCD is supporting research on the speech and language development of children with hearing loss, including those who use cochlear implants or hearing aids, those who pursue oral communication and education, as well as those who use manual communication. One of the anticipated benefits of cochlear implantation in children is improved acquisition of spoken language. Scientists supported by the NIDCD conducted a study to measure language achievement in children with cochlear implants. The study compared a group of children who had received cochlear implants and a second group who were using hearing aids. The results showed significant differences in English language achievement levels favoring the children using cochlear implants. Thus, improvements in speech perception and speech production seen in children using cochlear implants are being translated into improved language performance. Such early intervention with these children and the establishment of a strong language system will help to lessen and perhaps avoid the academic problems, particularly in the area of reading, which has historically been associated with this population.

OVERSIGHT OF NIH PEER REVIEW AND NIH-SUPPORTED RESEARCH

Mrs. Northup: I understand that all grant applications are reviewed by your department and then sent the appropriate institute for oversight over the grant project. Do provide any other oversight of the peer review process? Do you review anything in the general body of research that claims to be scientifically based? Do you provide any guidance to researchers, even those that aren't submitting NIH requests, on how to ensure that their research is sound and conducted appropriately? What can we do to ensure that those who claim to be doing "research" truly are doing rigorous scientifically peer reviewed research?

Dr. Ehrenfeld: CSR receives all applications for NIH and assigns the applications to the potential funding Institute/Center (IC). The Center manages the initial peer review of approximately 70% of the 46,000 grant applications submitted annually to NIH. A second level of review is performed at the assigned funding IC, under the guidance of the IC's Advisory Council.

A mechanism that draws upon input from a variety of stakeholders and representatives is used to oversee CSR's peer review process. Scientific Review Administrators are trained to conduct review committee meetings according to NIH policies and best practices. IC representatives regularly attend peer review meetings to monitor the review of applications assigned to their portfolio. The CSR Advisory Committee oversees all CSR policy matters and empanels subcommittees composed of representatives of the external research community to perform periodic evaluations of review meetings. Finally, CSR has OMB approval to conduct periodic surveys of both reviewers and applicants, to provide input for the review oversight process.

All applications received and reviewed by NIH are scientifically based. Research that is funded by NIH is regulated by the Office of Extramural Research in conjunction with the funding institute. Regulation of research not funded by NIH is not encompassed within the NIH mission.

While NIH does not specifically oversee research that it does not fund, CSR and the ICs perform extensive outreach activities within the general biomedical research community. These activities include attending professional and society meetings and visits to institutions to inform the research community of the NIH mission and research interests. Other outreach activities include education about the review process and how to write a grant application.

Training in ethical conduct of research is required of all NIH-supported trainees, and is generally extended to non-NIH supported trainees in research institutes and universities as well.

Only research funded by NIH falls under NIH regulatory jurisdiction. Research that is funded by NIH must first pass a rigorous, multi-tiered review process.

Research grant applications to NIH are not submitted by individual researchers, but rather by the universities or research institutions where the researchers, who develop the applications and will conduct the proposed research, are employed. Before an application can be considered by NIH, the institution must agree to support the applicant and oversee appropriate research conduct if the application is funded. Thus, oversight of NIH funded research is a shared responsibility between NIH and the researcher's institution.

MENTAL ILLNESS

Mrs. Northup: What sort of research do we have on the different levels of mental illnesses? Obviously there are severe mental illnesses and those that are less serious. Can you give us a breakdown of some of the varying kinds of mental illnesses and how many Americans are estimated to be afflicted with each of them?

Dr. Nakamura: Mental disorders are among the most persistent and disabling of all disorders, and recent international surveys indicate that in developed market economies, these disorders are second only to cardiovascular disorders as a leading cause of disability; unipolar depression ranks second behind ischemic heart disease as the most disabling specific condition. Co-occurrence of two or more mental disorders is frequently observed, and individuals with such co-morbidity typically have a more chronic course and utilize health services at a greater rate. NIMH is currently supporting an extensive series of studies in the U. S., in coordination with comparable international surveys, to gather updated prevalence rates of mental disorders and information on the types of disabilities and impairments in functioning that they produce in adolescents and adults.

Epidemiological surveys over the last 20 years have revealed that mental disorders are very common in the population, but that some people are afflicted with much more disabling, intrusive and persistent disorders than others. The recent Surgeon General's Report on mental illness estimated that in a 12-month period, approximately 23 percent of the U. S. adult population of 207 million adults have diagnosable mental disorders. Approximately 5.4 percent of adults in the U. S. suffer from serious mental illness (SMI), a term defined by federal regulations to apply to mental disorders that interfere with some area of social functioning. About half of all individuals with SMI suffer from even more disabling conditions, known as severe and persistent mental illness (SPMI); these conditions include schizophrenia, bipolar disorder, and severe forms of depression, panic disorder, and obsessive-compulsive disorder. The remainder of individuals with SMI have unipolar depression, anxiety disorders, eating disorders, and severe personality disorders.

Corresponding data for children and adolescents are less readily determined because it is sometimes difficult to distinguish disorders from normal developmental changes in behavior, and because various criteria are used to determine the degree of impairment in social functioning. The estimated overall prevalence is 11 percent (or 4 million children) when the criterion was significant impairment at home, at school, and with peers. It is 5 percent with a criterion of extreme functional impairment.

INTERAGENCY AUTISM COORDINATING COMMITTEE

Mrs. Northup: I am extremely interested in the Interagency Autism Coordinating Committee meeting that was held last November. Can you tell me some of the highlights of that meeting?

Dr. Nakamura: The Children's Health Act of 2000 (P.L. 106-310), Title I, Section 104, mandated the establishment of an Interagency Autism Coordinating Committee (IACC) to coordinate autism research and other efforts within the Department of Health and Human Services (DHHS). In April 2001, Secretary Tommy Thompson delegated the authority to establish the IACC to the National Institutes of Health (NIH). The National Institute of Mental Health (NIMH) at the NIH has been designated the lead for this activity.

The committee's primary mission is to facilitate the effective and efficient exchange of information on autism activities among the member agencies, and to coordinate autism-related activities. The Committee is made up of representatives of federal agencies who are working on autism issues, as well as public members. P.L. 106-310 specifies that parents or legal guardians of individuals with autism or other pervasive developmental disorders be appointed to the Committee. Such appointments are necessary and vital to the conduct of the committee's mission. Public members of the IACC help bring to DHHS the concerns and interests of members of the autism

community. The IACC serves as a forum and assists in increasing public understanding of the member agencies' activities, programs, policies, and research and in bringing important matters of interest forward for discussion.

The first IACC meeting was held on November 19, 2001, co-chaired by Dr. Steven E. Hyman (then director of NIMH), and Dr. Yvonne Maddox (Acting Deputy Director of NIH). The purpose of this inaugural meeting was to inform members about the various activities on autism across DHHS and other departments and to hear the concerns and priorities of the non-federal, public members. Presenters from NIH included Dr. Duane Alexander (NICHD), Dr. Stephen Foote (NIMH) Dr. Judith Cooper (NIDCD), Dr. Cindy Lawler (NIEHS), Dr. Audrey Penn (NINDS). Highlights of these presentations included a description of the Collaborative Programs of Excellence in Autism (CPEAs) sponsored by NICHD and NIDCD; an update on the development of the STAART Centers (Studies to Advance Autism Research and Treatment); and a description of activities of the NIH/Autism Coordinating Committee.

Updates from other federal agencies included presentations by Dr. Patricia Morrissey, Commissioner of Administration on Developmental Disabilities at the Administration on Children and Families; Dr. Henry Falk of the Agency for Toxic Substances and Disease Registry; Dr. Jose Cordero, Acting Director of the National Center on Birth Defects and Developmental Disabilities of the Center for Disease Control and Prevention; Dr. Kathryn Carbone of the Center for Biologics Evaluation and Research of the Food and Drug Administration; and Dr. Gail Houle from the Office of Special Education Programs in the Department of Education.

Public members discussed potential collaborations and private-public coordination of efforts. Presentations included those from Mr. Lee Grossman, President of the Autism Society of America, Mr. Jon Shestack, Vice President of Cure Autism Now, and Dr. Lucille Zeph, Director of the Center for Excellence in Developmental Disability Education, Research, and Service in the Center for Community Inclusion at the University of Maine.

An open session for public comment included participation of several parents of children with autism and representatives from advocacy groups including Safe Minds and the Autism Autoimmunity Project.

Finally, and importantly, several strategies were discussed for increasing communication and sharing of information on autism activities among IACC members.

Next meeting will be May 24, 2002, at the NIH. Information about IACC activities can be found at: http://www.nimh.nih.gov/events/interagencyautism.cfm.

NATIONAL CENTERS FOR AUTISM RESEARCH

Mrs. Northup: Where are we in terms of establishing new national centers for autism research?

Dr. Nakamura: The Children's Health Act of 2000 calls for the NIH to establish at least five centers of excellence in autism research. NIH began two separate efforts to get these centers established as soon as possible. First, NIH initiated a two-stage process of creating the new program of STAART (Studies to Advance Autism Research and Treatment) Centers. The first stage provides support, through Developmental Grants, to cultivate the field of investigators interested in autism research, and to position them well for stage two, which will be competition for comprehensive STAART Centers grants.

In April 2001, NIH issued a request for applications (RFA) on "Developmental Grants for Autism Centers of Excellence" (see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-01-013.html). This one-time solicitation, jointly sponsored by the NIMH, NICHD, NINDS, NIDCD and NIEHS, was designed to provide developmental grants to teams of investigators to enhance their ability to plan, organize, and demonstrate the feasibility of their autism research efforts. Under the developmental grant RFA, six grants were awarded by the targeted funding date of October 1, 2001. NIH made these awards to teams of investigators engaged in promising autism research at the University of California, Davis, M.I.N.D. Institute; Emory University, Atlanta; the University of Florida, Gainesville; the University of Utah, Salt Lake City; the University of Missouri, Columbia; and Washington University, St. Louis.

We anticipate that recipients of these developmental grants will apply this year for grants for full STAART Centers, and we anticipate funding successful applications for the STAART Centers in FY 2003.

Secondly, NIH released, in mid-June 2001, an RFA (see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-02-001.html) for investigators who already are conducting autism research and were prepared to apply for STAART Center support on an earlier timeline (application deadline 11/29/2001), without participating in the developmental grant process. These applications could request a maximum of $1.2 million per year in direct costs for up to five years. Review of these applications occurred in March 2002, and results of the scientific review are under consideration by participating NIH institutes. Successful applications will be funded in June 2002, with contributions from the NIMH, NICHD, NINDS, NIDCD and NIEHS.

An RFA for the second competition for STAART Centers is in preparation, and will be released to solicit applications for a receipt date in August 2002. Researchers who unsuccessfully applied for developmental grants or comprehensive center grants may submit a revised application for STAART Center support by the August 2002 deadline. New applicants also may apply for STAART Center support.

BEHAVIORAL TREATMENT THERAPIES FOR AUTISM

Mrs. Northup: What are the latest research showing regarding behavioral treatment therapies for autism?

Dr. Nakamura: Research shows that early, individualized, and intensive educational and behavioral interventions can result in improved outcomes for children with autism. The best evidence for efficacy is currently for interventions based on the principles of Applied Behavioral Analysis (ABA), which is a type of intensive behavioral treatment. In some cases, the improvement following ABA treatment has been reported to be impressive as children learn how to overcome, at least in part, the communication and social deficits typical of the autistic disorder. There is, however, controversy as to whether treatment can really 'normalize' children, that is, bringing them to a level of functioning comparable to children without autistic disorder. Other promising types of interventions are being developed and will need to be tested for efficacy. We still need to learn how to better match interventions to the child's specific characteristics and needs.

Several current initiatives include autism treatment research. The National Institutes of Health Autism Coordinating Committee (NIMH, NICHD, National Institute of Neurological Disorders and Stroke, National Institute on Deafness and Other Communication Disorders contributing) awarded seven grants in September 2001 to support the development and/or refinement of treatments for autism, four of which were tests of behavioral treatments. The STAART Centers grants that will be awarded in FY02 and FY03 will include treatment studies including behavioral treatments; it is expected that the four institutes named above will contribute funding. NIMH is currently funding Research Units on Pediatric Psychopharmacology (RUPP) and is reviewing applications for Research Units on Pediatric Psychopharmacology and Psychosocial Intervention (RUPP-PIs); both of these networks include a strong emphasis on autism treatment.

TREATMENT ADHERENCE

Mrs. Northup: I am very interested in problems associated with keeping the mentally ill on their medication. What has your research shown about effective strategies for allowing the mentally ill to consistently self-regulate their own medicine and what can you tell us about new prescriptions that perhaps could be implanted for a time released delivery of medicine?

Dr. Nakamura: Current theories about treatment adherence in mental illness suggest that several factors influence a patient's cooperation with prescribed medications. Among these are the individual's health goals and priorities, ability to understand and remember medication instructions, experience of medication side-effects, logistical barriers to obtaining medications, the availability of cues and reminders in the natural environment that trigger medication activities, and the alliance

between the health care team and patient to facilitate adherence. NIMH-supported researchers are testing a variety of strategies for improving effective medication self-administration in schizophrenia, major depression, and HIV/AIDS. Promising methods include placing mechanical and electronic memory aids in the patient's home, and using automated telecommunication systems to help patients monitor appropriate use of medications. In addition, private-sector pharmaceutical companies are now developing longer-acting antipsychotic and antidepressant medications, although the impact of these preparations on medication adherence, which are injected rather than implanted has yet to be determined. The recent NIMH program announcement "Research on Adherence to Interventions for Mental Disorders" (PA-00-016) solicits additional scientific efforts to integrate findings and methods from the behavioral and neurosciences with adherence-enhancing interventions for mental disorders. Investigator-initiated proposals to test the impact of time-released medications on adherence to mental disorder treatments would be welcomed under this announcement.

NIDA'S PREVENTION AND TREATMENT RESEARCH INVESTMENT

Mrs. Northup: How much of your work is dedicated to drug abuse treatment and how much to drug abuse prevention?

Dr. Hanson: All of NIDA's research is aimed toward improving treatment and prevention interventions. Treatment accounts for 51% of our research and prevention accounts for 49% of our research.

SHARING RESEARCH FINDINGS WITH DRUG MANUFACTURERS

Mrs. Northup: What are you doing to share what you learn about how individuals abuse drugs with drug manufacturers in order to prevent situations like what is happening with Oxycontin?

Dr. Hanson: NIDA has taken a leadership role in alerting the public, policy makers, pharmacists and drug manufacturers about the disturbing increases in prescription drug abuse. We have issued a number of publications, testified at hearings, encouraged new research on this topic, and have held a series of public events that have included representatives from drug companies.

Additionally, we continue to support activities to further understand the abuse potential of drugs of abuse. For example, under NIDA's Cooperative Research and Development Agreements (CRADA) we assess abuse liability and other ways to minimize abuse with the companies with whom we work. Also, upon request from a pharmaceutical company we discuss the abuse liability of a compound in the company's development portfolio, how to minimize abuse through formulation considerations, and how to assess the medications for scheduling under the Controlled Substances Act (CSA).

We also have a contract with the Medical College of Virginia to receive and specifically test compounds from drug companies (and also government agencies and academic sources) for their abuse liability and analgesic properties. These data are provided to the drug companies, to NIDA (in quarterly, annual and final reports), and published annually in the NIDA-College on Problems of Drug Dependence Proceedings. An Abuse Liability Contract with Johns Hopkins University allows us to test abuse liability of stimulant compounds submitted by academic institutions, individual investigators, private sectors, a governmental agency such as Drug Enforcement Agency (DEA) and the pharmaceutical industry. The data obtained are reported in triannual reports and are available upon request. The information is used both domestically and internationally for drug scheduling purposes. Additionally, we are also currently working closely with the DEA on assessing abuse liability of, for example, MDMA-like drugs that are being distributed illegally.

To provide just one concrete example of how NIDA shares drug abuse research findings to make the safest medications possible with low diversion potential, NIDA worked closely with Reckitt Benckiser, a CRADA partner, to develop buprenorphine/naloxone, a new medication to treat opiate addicts. Through NIDA's clinical pharmacology efforts, we were able to determine the appropriate best formulation ratio of buprenorphine to naloxone (a narcotic antagonist) to reduce the risk of overdose, as well as to reduce needle sharing and its attendant infectious disease risk. Patients enrolled in clinical trials using this formulation were successfully treated. This exemplifies how NIDA works with pharmaceutical companies to reduce abuse liability and possible mortality and morbidity.

PRESCRIPTION DRUG ABUSE

Mrs. Northup: Has your research shown any differences in abuse patterns and in effects on individuals between prescription drug abuse and abuse of illegal substances?

Dr. Hanson: Most people who take prescription medications take them responsibly; however, the nonmedical use or abuse of prescription drugs remains a serious public health concern. Certain prescription drugs, opioids, central nervous system (CNS) depressants, and stimulants when abused, can alter the brain's activity and lead to dependence and possibly addiction. This is why we say prescription drugs can be as addictive as illegal substances. Of course, the particular brain effects differ from one substance to another and the social effects also vary according to the substance. But the basic concept holds that all addictions have similar presentations. Although prescription drug abuse affects many Americans, some trends of concern can be seen among older adults, adolescents, and women. In addition, health care professionals including physicians, nurses, pharmacists, dentists, anesthesiologists, and veterinarians may be at increased risk of prescription drug abuse because of ease of access, as well as their ability to self-prescribe drugs. In spite of this increased risk, recent surveys and research

in the early 1990s indicate that health care providers probably suffer from substance abuse, including alcohol and drugs, at a rate similar to rates in society as a whole, in the range of 8 to 12 percent.

RITALIN AND SUBSTANCE ABUSE

Mrs. Northup: What has your research shown about the relationship between children who take Ritalin and their propensity for substance abuse?

Dr. Hanson: Currently, data are conflicting regarding the role of stimulant medication on later substance abuse. However, the preponderance of evidence so far suggests that prescription stimulant medication has a protective effect against later substance abuse. The question as to whether prescription of stimulant medications such as Ritalin during childhood alters the risk for later substance abuse is very timely and of great interest to NIDA. In fact, recently funded research projects will be able to shed light on this very important public health question. Several complex issues complicate this area of research. Children with attention deficit hyperactivity disorder, for which Ritalin is frequently prescribed, often have other concurrent psychiatric disorders that put them at risk for substance abuse. Therefore, further study is needed to distinguish between psychiatric and medication risk factors. Studies currently underway will be well-positioned to answer these pressing questions.

SHARED RESOURCES

Mrs. Northup: What kind of resources do you provide that can be shared by investigators?

Dr. Vaitukaitis: The NCRR provides a variety of resources that can be shared by investigators. In fact, NCRR's primary strategy for leveraging Federal research dollars is to encourage investigators and institutions to share scarce or expensive research resources, including sophisticated instrumentation and biologic models. These shared resources include the nationwide network of about 80 General Clinical Research Centers, 8 National Primate Research Centers, 66 Biomedical Technology Resource Centers, and many other resources, including biorepositories. The shared resources supported by NCRR provide a fertile environment to stimulate collaborations among investigators.

SHARED RESOURCES

Mrs. Northup: How do you determine who should receive new medical and laboratory equipment?

Dr. Vaitukaitis: Applications for new medical and laboratory equipment are peer reviewed, just as applications for research grant support undergo peer review. One of the primary review criteria is the plan for sharing this expensive equipment among a

group of at least three investigators. The equipment must also be available off-the-shelf, required for use by NIH-supported investigators, with housing and maintenance supported by the host institution.

Instrumentation is also supported as part of some of our center grants; these requests are also peer-reviewed along with the parent grant.

AIDS CENTER GRANTS

Ms. Pelosi: The NIMH AIDS center grants (currently at UCSF, UCLA, Wisconsin, Columbia, and Yale) have been important and pivotal in moving forward the field of HIV prevention and care research, especially as it relates to mental health. It is my understanding that recently imposed caps on funding for these centers are creating unforeseen problems. Is NIMH willing to reconsider the caps imposed on these centers? What steps are being made to ensure that these centers have sufficient resources to support the ongoing research at their respective institutions?

Dr. Nakamura: The NIMH AIDS Centers Program has been very successful in providing an environment that strongly supports state-of-the-art AIDS research. The initial funding mechanism for these centers included funding for primary research projects as well as for the scientific cores that provided infrastructure support necessary to carry out the research. Recently, NIMH has converted the centers' mechanism to one that provides funding for the infrastructure support only. The primary research is submitted, reviewed, and funded by NIMH independently from the Center. This has many advantages. The Centers are able to provide infrastructure support to all research being conducted, facilitating collaboration across many disciplines of science, a critical need in the current state of the AIDS epidemic. Independent submission of individual research projects allows the research to undergo the rigorous peer review necessary to assure that it is of the highest quality. NIMH regards the current cap of $2,000,000 as reasonable and does not at present plan to raise it. Rather, we are interested in expanding the Centers program and adding one or more Centers to support a broader range of scientific effort.

NIMH program staff have worked with investigators to assure that the appropriate competitive mechanisms are available to support the successful ongoing research at the various institutions. This has resulted in the modification of the structure and the monetary cap of existing mechanisms. NIMH staff will continue to work creatively to assure that resources are available to support successful research at these institutions.

ACCESS TO CARE AND SUBSTANCE ABUSE TREATMENT

Ms. Pelosi: Since 1997, San Francisco has been committed to providing treatment upon request to active drug users.

San Francisco's experience has resulted not only in an increase in the number of treatment service slots available, but also in knowledge development about effective treatment responses, evidence-based practices, and best practice guidelines and

standards. Has NIDA done any research on the relationship between access to care and effective substance abuse treatment?

Dr. Hanson: Yes. NIDA, through its health services research program, supports a substantial portfolio of research on the relationship between access to care and effective drug abuse treatment. This includes a research grant to the University of California at San Francisco funded in 1999 to investigate San Francisco's drug abuse treatment on demand initiative and to identify what its most effective features are. One of the key questions that researcher Dr. Joseph Guydish hopes to have answered within the next 18 months is: "To what extent can providing treatment-on-demand eliminate barriers such as costs, waiting lists, and limitations on types of treatment options available? " This five-year study explores the impact of increased community treatment capacity, enhanced service efficiency, and more lasting treatment results, that treatment-on-demand might have on public health costs.

In general, NIDA's research on access to drug treatment focuses on treatment system organization and management, and on treatment system financing. The organization and management portfolio includes studies to modify treatment or treatment systems to improve access, including research to improve assessment of problems. Examples of research supported include improving criteria for matching patients to treatment, research to reduce barriers to treatment entry, research on access to care for special populations such as welfare recipients, and research on treatment system structure. NIDA supports more than 20 research grants in this area.

Treatment system financing studies include research on how managed care affects service availability and utilization, For example, researchers are examining the costs of drug treatment under private insurance. NIDA supports more than a dozen grants in this area.

GCRC PILOT STUDIES

Ms. Pelosi: It has been almost two years since the NCRR Advisory Council approved the concept of providing "seed money" for General Clinical Research Center-based pilot projects. This Subcommittee urged you to move forward with this approach in report language accompanying our FY 2000, 2001 and 2002 bills. How many centers have received pilot study support and how many pilot projects have been funded? What is the total amount of funding that has been provided for this purpose?

Does each GCRC receive an equal amount for pilot projects? If not, how are the funds distributed?

It is my understanding that a number of other programs are funded out of the GCRC appropriation. Could you tell me why this is, what those programs are, and how much money each receives?

Dr. Vaitukaitis: Pilot studies on GCRCs were phased in during FY 2002 with the intent that all GCRCs would be able to request up to $100,000 per annum for their support within 2-3 years. We become aware of pilot projects when GCRCs make a specific request for new funds and, in FY2002, 27 GCRCs made such requests. GCRCs are also permitted to rebudget funds internally to support pilot projects. Approximately 32 pilot projects were funded in FY2002 in the 27 GCRCs that applied for new funds for the purpose.

A total of $645,000 was made available in FY2002 but internal rebudgeting may allow for the funding of additional pilot projects. The full number will not be known until the Centers submit their annual reports..:

Each GCRC does not receive an equal amount for pilot projects. The amount received depends first on the participation of the GCRC and on the local approval of the pilot projects by an Advisory Committee. By FY2003 we anticipate making new funds available for 2 pilot projects per center. Centers may increase their number of pilot projects beyond this if they are able to rebudget funds internally.

Funds reported as "GCRC funding" include awards for clinical research career development, clinical curriculum development, and the new clinical loan repayment program, in addition to support for the GCRCs themselves. All activity reported as GCRC funding goes to or directly benefits the GCRCs, although through different mechanisms.

By far, one of our greatest priorities for clinical research is the training of future clinical investigators. The research careers program accounts for the largest amount of GCRC funding in a mechanism other than the Centers line; formerly, funding for research careers was done through supplements to the GCRCs, and now, that mechanism has been replaced by the NIH wide K-23 program. NCRR is one of the largest supporters of clinical research career development. The amount included in the FY 2003 President's Budget request for clinical research careers (including curriculum development) is $26.6 million. NCRR's clinical loan repayment program will total $3.5 million in FY 2003, with all those funds going to researchers affiliated directly with the GCRCs. Other small amounts attributable to the GCRC budget include the costs of peer review of the GCRCs, conferences supported by the GCRCs, and funding for ethics training.

SCHIZOPHRENIA

Mrs. Lowey: Dr. Nakamura, in 1998, NIMH was reorganized to better address the major public health needs associated with severe mental illnesses. How is NIMH studying schizophrenia under the new structure?

Dr. Nakamura: The recent reorganization of the NIMH successfully distributed schizophrenia-related grants throughout the Institute to ensure cross-fertilization with cutting-edge research in diverse areas. In particular, the new structure has facilitated translational research—that is, the application of basic research in neuroscience, behavioral science, and new technologies to research on pressing clinical and health services research issues. This approach is consistent with attempts throughout NIH to ensure that research contributes maximally to public health issues. In the neuroscience area, for example, there is a large technology transfer program which funds advanced research in such areas as neuroimaging, genetics, and the molecular and cellular basis of neuronal signaling. Because this research is housed in the same division as the portfolio for neuroscience research in schizophrenia, program staff are ideally situated to ensure that new developments are rapidly applied to clinical research. The Silvio Conte Centers for Translational Research in Neuroscience represent a prime example of this approach, by explicitly requiring innovative applications of basic science to hypothesis-driven clinical research. To date, four of these centers have been funded in the area of schizophrenia (as well as other center grants in different areas of psychopathology), integrating studies of neurotransmitters, brain circuitry, and perceptual and cognitive functioning.

Behavioral research on schizophrenia has similarly been facilitated by the new structure and the new translational research approach. New psychosocial approaches have been developed to help patients deal with their disabilities, based on basic behavioral research in such areas as cognitive science, learning, and emotion. For instance, one promising new strategy involves engineering the environment to provide cues for taking medication, remembering appointments, and performing everyday tasks. Other recently funded grants are based upon principles of learning and attention, and are designed to improve the ability of patients with schizophrenia to learn and remember important skills for job performance and daily functioning. The new NIMH structure has also facilitated the explicit integration of different disciplines such as neuroscience and behavioral research. For example, one recently awarded grant will assess a psychosocial treatment for cognitive functioning, in part, by functional neuroimaging to document the ways in which the brain is actually changed by the learning process. Finally, centers for translational research in behavioral science have also been approved, and are expected to yield the same benefits for integrative behavioral approaches to schizophrenia as the Conte centers have done for neuroscience.

The new structure has also facilitated the design of powerful clinical trials to assess the effectiveness of new treatments for schizophrenia. The CATIE trial (Clinical Antipsychotic Trials of Intervention Effectiveness), for instance, has been designed

specifically to evaluate the effectiveness of the newer, "atypical" antipsychotic medications in the real-world treatment of schizophrenia, without excluding certain types of patients (for example, those with substance abuse or uncooperative behavior). At the same time, the programmatic integration of schizophrenia with other disorders meets a range of public health needs; for instance, the CATIE trial design has allowed one portion of the study to include a test of the same medications for their use in controlling psychotic symptoms in Alzheimer's disease. Finally, the Institute's new organization permits better consideration of schizophrenia research with respect to special populations. For instance, as research on aging is distributed throughout the portfolio, program staff can more easily integrate research on schizophrenia in late life with other research bearing on common problems of the elderly, such as care in nursing homes and assisted living facilities, mood disorders of dementing conditions, and burden on caregivers. Overall, the 1998 reorganization has positioned the Institute to make effective use of new research advances both to address the fundamental causes of schizophrenia, and to offer improved treatments and ways of coping in everyday life for patients and their family members.

NEW TREATMENTS FOR MENTAL ILLNESS

Mrs. Lowey: Dr. Nakamura, in the last decade, many new treatments have been developed for severe mental illnesses. Yet, most individuals with these illnesses do not have access to these new treatments. What efforts are underway to ensure that the improved treatment interventions being developed will be available to those who desperately need them? Is NIMH collaborating with SAMHSA and CMHS on these efforts?

Dr. Nakamura: The NIMH has a specific program in dissemination and implementation research that sponsors grants to find ways to ensure that effective treatments are implemented in community practice. Ongoing activities in this program include a new program announcement calling for grants in this area; new funding mechanisms to promote this area (including one jointly issued with CMHS on Children's Services); and sponsorship of workshops and conferences to foster new research ideas in this area. One recent workshop focused on implementing evidence-based practices into the public mental health sector. In addition, the NIMH supports research on new ways (e.g., telemedicine) to deliver services to areas that have limited access to mental health services (i.e., rural and frontier areas).

NIMH has collaborated with SAMHSA, especially CMHS, on issues related to improving the implementation of new treatment interventions. CMHS representatives were actively involved in recent workshops and discussions about joint funding of future projects. Other collaborative efforts are underway to foster new research opportunities and implementation strategies.

CLINICAL RESEARCH ENHANCEMENT ACT

Mrs. Lowey: Dr. Vaitukaitis, as you know, I am very interested in issues related to clinical research. In fact, I authored the Clinical Research Enhancement Act (CREA) to help improve clinical research in the U.S. and to bring new scientists into clinical research. Could you please update me on the progress NCRR is making in implementing CREA?

Dr. Vaitukaitis: The Center for Scientific Review (formerly DRG) has established two new study sections, Clinical Oncology and Clinical Cardiovascular Sciences, that are devoted to the review of clinical and patient-oriented research. In other study sections, clinical topics and patient-oriented research have been clustered so as to constitute approximately 30 percent of the application load, and about 30 percent of the reviewers have clinical expertise whenever possible. The current reorganization of CSR's study sections is involving representatives from all stakeholders, including researchers from all clinical fields. Their input is helping to design a complete new set of study sections, to be implemented over the next three years.

Peer review groups that evaluate applications for career awards and fellowships have been established in most of the Institutes and Centers, as well as in CSR. These groups include individuals who are exceptionally qualified to appraise the merits of potential clinical research training and research grant proposals.

In addition to the General Clinical Research Centers (GCRCs), NCRR supports multiple resources for clinical research, such as the National Gene Vector Laboratories, the National Disease Research Interchange, Human Islet Cell Resources, Genotyping Resources, Microarray Resources, Bioinformatics Regional Resources and Institutional Cores, Clinical Trials web-based network for Cystic Fibrosis, Biomedical Informatics Research Network and Research Subject Advocates. The resources listed are available to any qualified investigator, independent of whether their institution has an NIH-supported GCRC. Since FY 2000, funding for the GCRCs has increased from $198.6 million to $271.6 million in FY 2002. NCRR has established a new GCRCs at University of Maryland and expects to start a GCRC at the University of Miami.

In collaboration with the San Diego Supercomputer Center, the National Science Foundation, and several universities, NCRR established the Biomedical Informatics Research Network (BIRN). The BIRN was established in FY 2001 to provide a high-tech network dedicated to collecting and sharing data on human brain morphology, through brain mapping and imaging in animals and humans. The BIRN currently includes two GCRCs that are co-located with NCRR imaging centers, and in the future, this model will be extended to all NCRR resource sites for a full range of biomedical studies along with wireless access for investigator outreach.

A cyber-based network, CFnet, was established a few years ago by NCRR in partnership with the Cystic Fibrosis Foundation as a pilot study to ascertain whether phase 1 and 2 clinical trials could be facilitated across several GCRC sites with web-based data handling. This effort has been so successful that CFnet will be extended to a total of 20 GCRC sites and a comparable network will be established for the eight minority-serving medical schools to enhance their participation in clinical trials that focus on health disparities and other collaborative studies.

NCRR has replaced its Clinical Associate Program, formerly funded as competitive supplements to NCRR GCRCs, with the Mentored Patient-Oriented Research Career Development Award Program (K23). The purpose of this award is to support the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. The award provides support for three to five years of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research. NCRR has also established a Mentored Clinical Research Scholar Program using the K12 mechanism to provide up to five years support in a mentored environment for clinical fellows or junior faculty interested in pursuing patient-oriented research. The purpose is to support an institutional career development program for physicians and dentists to develop the skills to become independent patient-oriented clinical investigators. The first grants will be made in FY 2002. Mid-Career Investigator Awards in Patient-Oriented Research (K24 award) provide support for clinicians, giving them protected time to devote to patient-oriented research, and to act as mentors for beginning clinical investigators. The K30 award, supported by many of the NIH Institutes and Centers, provides for the development or improvement of core courses for instruction of clinical investigators.

NCRR expects to make 15 awards for a total of $1.5 million under the Clinical Research Loan Repayment Program, beginning in FY 2002. Funds are available to support at least 250 2-year contracts across NIH in FY 2002, and approximately 500 contracts in FY 2003. Applications have been received, and review is pending.

YOUTH SUICIDE

Mr. Kennedy: The increasing suicide rate in young people and the high suicide rates among individuals with severe mental illnesses is alarming - reaching 15 percent of afflicted individuals with schizophrenia, bipolar disorder, and major depressive illness. What efforts do you have underway to increase our understanding of suicide and to improve our recognition of individuals at imminent risk and improve treatment?

Dr. Nakamura: Suicide is a tragic and potentially preventable public health problem. Over 90% of youth who die by suicide had a mental disorder. About two-thirds had a depressive disorder, and a quarter to a third had made a prior suicide attempt. Substance use disorders are also often present, particularly among older teens. While schizophrenia carries increased risk for suicide, it is associated with few youth suicides because the onset rate is later among young adults. Bipolar disorder has been found to be present among youth suicide decedents in some studies but not others.

NIMH has worked to increase applications that test interventions aimed at reducing risk factors (e.g., depression, conduct disorder) as well as treatments focused on youth at imminent risk. An NIMH program announcement, Interventions for Suicidal Youth, cosponsored by the National Institute on Drug Abuse (NIDA), continues to receive applications from both mental health and substance use researchers. After a series of workshops, NIMH staff along with outside bioethics and suicide research experts developed documents for researchers that describe safe and ethical approaches to including suicidal youth in treatment studies. A document is available on the NIMH website, and a summary has been submitted to the Internal Review Board (IRB) journal. An NIMH-commissioned review of youth suicide measures, also available through the NIMH website, provides researchers with guidance for selecting measures of risk and protective factors, as well as suicidality. The growing number of research and career development awards are evidence that these efforts have reduced barriers to youth suicide research. We continue to work with the Office of the Surgeon General, SAMHSA, HRSA, the CDC, and other NIH Institutes (NIDA, National Institute on Alcohol Abuse and Alcoholism, National Institute of Child Health and Human Development) through joint scientific meetings and shared web-based resources in order to continue to increase the research base for youth suicide prevention.

COLLABORATION WITH SAMHSA

Mr. Kennedy: SAMHSA is in the process of reverting to its core mission of developing services models has divested itself of some of its research and evaluation of services programs. How are NIDA, and NIMH going to collaborate with SAMHSA on research dealing with drug abuse prevention, effective services and relay the results of research to "front line" providers?

Dr. Nakamura: As part of an effort to strengthen both the research and service missions of the Federal Government with respect to mental health and substance abuse, a comprehensive and important bipartisan law reorganized the former Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) in 1992 [P.L. 102-321]. The research components of ADAMHA's three organizational entities - NIMH, NIAAA, and NIDA – were merged into the NIH. This legislation mandated that the three Institutes obligate at least 15 percent of their research budget for health services research. The service-oriented arms of ADAMHA became the current Substance Abuse and Mental Health Services Administration (SAMHSA). Over time, SAMHSA has developed its own portfolio of knowledge development grants. As a result, both agencies have been involved in health services research to examine factors around the delivery of health services, including research on implementing evidence based practices in real world settings.

The mission of the NIH institutes is to lead the Nation in bringing the power of science to bear on their respective areas of research. This charge has two critical components: first, the strategic support and conduct of theoretically driven research across a broad range of disciplines including health services research, and second, the rapid and effective dissemination of the research results to improve treatment and prevention. SAMHSA's mission is to improve the quality and availability of prevention, treatment, and rehabilitative services in order to reduce illness, death, disability, and cost to society resulting from substance abuse and mental illnesses.

To the extent possible, we at NIH collaborate with our colleagues at SAMHSA to ensure that research funded by NIDA, NIMH, NIAAA and other relevant Institutes is disseminated to the field. In line with the FY 2003 Budget, NIH and SAMHSA will continue meeting to collaborate more fully in mental health and substance abuse prevention and treatment and better clarify the roles of each agency. This increased collaboration is critical to shorten the time period between research advancements and improvements in the delivery of services.

Given SAMHSA's recalibration of its core mission, NIDA, NIMH, and NIAAA intend to send notices of all of their funding opportunities (Requests for Applications, Requests for Proposals, and Program Announcements) to SAMHSA's current grantees, to encourage them to apply for NIH grants. The Institutes will invite them to NIH workshops, conferences, symposia, and other meetings that will help them develop NIH grant applications.

The NIMH has a well-developed program in mental health services research that started prior to its joining the NIH. This program sponsors research on topics including the cost-effectiveness of specific mental health treatments, the economic impact of mental disorders, innovative models for assessing and treating mental illness in primary care settings, and research on ways to increase the adoption of appropriate mental health services in every day clinical settings. NIMH has collaborated with SAMHSA to fund research on its demonstration projects; in these efforts, NIMH has paid for the research

component while SAMHSA has funded the delivery of services. We anticipate that knowledge gained through NIMH-funded dissemination research studies will continue to yield general principles that will be of great utility to the mental health and substance abuse fields in conveying the results of research to health care providers.

With respect to substance abuse prevention strategies and methods, NIDA's prevention portfolio is particularly robust and has provided communities across the country with science-based prevention principles and strategies that can be used to assess local drug abuse problems and to develop comprehensive, effective drug abuse prevention strategies. NIDA has just launched a new National Prevention Research Initiative (NPRI) in order to take this prevention research to the next level, to ensure the successful implementation of science-based interventions in communities and to address some new unstudied tough questions that focus on issues such as the more immediate factors that influence an adolescents' decision to use or not use drugs. The NPRI will involve a number of partners working together to test the effectiveness of new and existing science-based prevention approaches in different communities, while simultaneously studying how best to adapt the programs for local communities. Another component of this Initiative will consist of transdisciplinary prevention research centers, which will foster collaborations between neuroscientists, behavioral scientists, cognitive scientists, and drug abuse prevention researchers to address knowledge gap areas and how to approach the scientific questions in drug abuse prevention research in new ways. A basic science component will also help to attract new researchers to this important area who could apply basic science knowledge to the development and improvement of prevention interventions.

This multi-faceted approach will bring together researchers from a variety of disciplines as well as state and local policy makers to work together to more thoughtfully and innovatively bring science-based interventions to the community level. As noted, NIDA encourages potential grantees who may have participated or have gained expertise while being supported by SAMHSA's Center for Drug Abuse Prevention to apply for NIDA funding or to establish relationships with NIDA researchers. NIDA also will provide technical assistance to develop SAMHSA grantees' research capabilities and grant writing skills. Grantees with expertise on how best to deliver prevention services to communities will be useful to our Nation's prevention endeavors.

COORDINATING EPILEPSY RESEARCH EFFORTS

Mr. Kennedy: As you know, over 2.5 million Americans are diagnosed with epilepsy, including at least 750,000 with intractable epilepsy. The annual direct and indirect costs of epilepsy are estimated to exceed $12.5 billion. Given this huge impact, it is evident that the funding levels for epilepsy research lag far behind what is needed, despite the encouragement of Congress over the past few years to intensify efforts to cure the disease.

The FY02 Labor-HHS Bill contained congressional Report Language encouraging the establishment of an Interagency Coordinating Council to coordinate research efforts in epilepsy between the NIMH, the National Institute on Aging, the National Human Genome Research Institute, the National Institute of Neurological Disorders and Stroke, and the National Institute of Child Health and Human Development. How do you envision taking a leadership role in coordinating the efforts of these various Institutes? How do you envision these cross-agency efforts furthering the search for a cure?

Dr. Penn: The National Institute of Neurological Disorders and Stroke (NINDS) is the lead NIH Institute for epilepsy research, but several other NIH Institutes also fund epilepsy related projects, including the National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), the National Institute for Child Health and Human Development (NICHD), and the National Human Genome Research Institute (NHGRI). NINDS is working with these Institutes to coordinate epilepsy research efforts, including their involvement, as appropriate, in the implementation of the research benchmarks developed as a result of the March 2000 conference, "Curing Epilepsy: Focus on the Future." This includes joint sponsorship of workshops and conferences, joint funding of initiatives, and periodic meetings to identify and discuss areas of common interest and opportunities for collaboration. NINDS has already initiated such efforts. For example, NHGRI is participating in a recent workshop on molecular analysis of complex genetic epilepsies; NIA and NIMH are cooperating with NINDS in a Request for Applications entitled "Gene Discovery for Neurological and Neurobehavioral Disorders" which was directly relevant to the Epilepsy Benchmarks for discovery of genes that predispose individuals to epilepsy; and similar cross-NIH efforts are underway on topics such as gene therapy.

NINDS also recognizes the importance of working with patient advocacy groups. The March 2000 conference on curing epilepsy represented a cooperative effort by NIH, working together with the Epilepsy Foundation, the American Epilepsy Society, Citizens United for Research in Epilepsy (CURE), and the National Association of Epilepsy Centers. The development of the Benchmarks was also a cooperative effort and we are continuing along those lines as we implement the benchmarks.

Central to the concept of the Benchmarks is the belief that they are milestones for the entire epilepsy community. Thus, as cited above, NINDS plans to coordinate with other NIH Institutes and Centers efforts to implement the Benchmarks. Additionally, we plan to include the epilepsy professional organizations, and the epilepsy patient community in research activities. All of these entities must work collaboratively if the goals are to be reached.

PARKINSON'S DISEASE

Mr. Kennedy: Your budget justification mentions the "Fast Track" grants that are being awarded by NIDCD on Parkinson's Disease. In particular, you mention how Parkinson's Disease degenerates nerve cells in the area of the brain that is critical for control of movement and how as the disease progresses their can be serious impairments of concern to NIDCD such as speech and swallowing difficulties. For NB4H there is interest in the disease in as well, including the onset of depression.

I commend the NIH partnership on Parkinson's that is a collaboration of NIDCD, and NIEHS (National Institute of Environmental Health Sciences) and NIMH. The fast track process aims at supporting the research for a cure, cause, and improved treatment strategy on Parkinson's.

Dr. Nakamura and Dr. Battey, would you both explain for me how this collaborative grant program is progressing at each of your institutes and some of the breakthroughs that you are working for on Parkinson's Disease?

Dr. Nakamura: The NIMH has a special interest in the cognitive and emotional concomitants of Parkinson's Disease as part of our ongoing commitment to addressing mental health problems in all populations. Degeneration of a part of the brain called the substantia nigra, which is the hallmark of Parkinson's Disease, leads to major changes in the same brain chemistry and brain pathways that have been implicated in causing depression and cognitive decline in patients with mental illnesses. Likewise, some treatments for Parkinson's Disease can provoke psychiatric symptoms like hallucinations or mood disorders, just as some treatments for psychiatric disorders can provoke Parkinson's-like motor rigidity. Given these similarities, the NIMH is committed to promoting research that elucidates the common pathways and mechanisms underlying depression, hallucinations and cognitive decline as they occur in Parkinson's Disease and mental illness. As a participating institute in the Fast Track R21 program, we recently funded 2 grants designed to investigate potential mechanisms underlying cognitive problems in patients with Parkinson's Disease that promise to clarify brain pathways and treatment mechanisms. The NIMH and the NINDS are currently evaluating applications on the mechanism of action of deep brain stimulation, a common treatment for Parkinson's Disease that can provoke emotional symptoms, for possible future funding. Finally, the NIMH has and will continue to actively participate in the NINDS-led Parkinson's Disease Research Consortium, which recently identified non-motor symptoms such as depression and dementia, as major priorities for future initiatives.

Dr. Battey: NIDCD was one of the Institutes to co-sponsor the solicitation for fast track applications focused on Parkinson's Disease (PD). Nine applications were identified as relevant to the mission of NIDCD (dealing with speech and swallowing in people with PD). Three of the nine were reviewed favorably and found to be meritorious of funding (which has recently begun or will begin shortly). One grant will look at the use of Personal

Data Assistants to enhance generalization of a specific speech and voice treatment program for individuals with PD. Another grant will examine the effectiveness of a specific intervention program in improving swallowing, which is often impaired in individuals with PD. The third and final grant will examine the effect of auditory feedback on improving the speech of persons with PD. In addition to these grants, NIDCD encourages and supports other research studies focused on improving our understanding and treatment of the voice, speech and swallowing problems associated with PD.

APHASIA

Mr. Kennedy: Too many families, has a history of stroke. Stroke continues to be the No. 3 killer in the United States and a leading cause of permanent disability.

This year 600,000 Americans will suffer a stroke and nearly 170,000 will die. An estimated 4.6 million Americans live with the consequences of stroke.

An estimated 1 of 4 stroke survivors is permanently disabled. Stroke will cost the nation an estimated $50 billion in medical expenses and lost productivity this year.

As I understand it, stroke usually does not cause hearing loss, but stroke survivors may have aphasia-problems understanding speech and trouble saying what they are thinking. Aphasia affect the abililty to talk, listen, read and write. Please tell this Committee what research is your institute supporting to make progress against aphasia?

Dr. Battey: Aphasia is a language disorder that results from damage to portions of the brain that are responsible for language. Aphasia research is providing new ways to evaluate and treat these language disorders, as well as to further our understanding of the function of the brain regarding language and language disorders. Brain imaging techniques are helping to define function, determine the severity of brain damage, and predict the severity of the aphasia. NIDCD supported scientists recently have documented reorganization of brain activity after treatment for acquired reading disorders following stroke. The central goal of aphasia therapy is to improve an individual's ability to communicate by helping the person to use remaining abilities, to restore language abilities as much as possible, to compensate for language problems, and to learn other methods of communicating. NIDCD-supported scientists are designing and studying the efficacy of behavioral treatments for a variety of language and cognitive disorders associated with aphasia. The use of a computer-assisted visual communication system to assist individuals with aphasia who are unable to produce or comprehend language is being studied. Promising new drugs that may improve the rate of language recovery administered shortly after some types of stroke are being investigated as ways to reduce the severity of aphasia. Finally, NIDCD will be assembling a group of cutting-edge scientists at a workshop in May of this year to identify research needs and opportunities in the area of the role of neuroimaging in the study of aphasia recovery and rehabilitation.

NIH FIRE PROTECTION MASTER PLAN

A PROGRAM FOR CORRECTING FIRE AND LIFE SAFETY DEFICIENCIES ON THE NIH CAMPUS AND THE NIHAC

INTRODUCTION

Many major fire protection systems on the NIH Bethesda campus and the NIH Animal Center at Poolesville have deteriorated over the years to the point of marginal reliability. This is due in part to the expansion of various systems, in order to accommodate growth, without adequate planning for the future. Furthermore, many of our buildings were constructed without consideration to the National Fire Codes and/or any of the model building codes. These same facilities have, over the years, received numerous modifications and alterations at which time many fire protection features (both active and passive) have been seriously compromised. While protection of life is paramount in the NIH safety program, it is also critical that the ORS provide state-of-the-art protection to the research facilities occupied by NIH employees. Exquisite and expensive scientific equipment, irreplaceable research materials, data, animals and other crucial resources are absolutely critical to the research mission of the NIH and must be protected from fire.

In developing an *NIH Fire Protection Master Plan*, it is difficult to establish priorities when considering the protection of life and property. With so many serious deficiencies previously identified by the Division of Safety, it is now an onerous task to decide which facility or major fire protection system is the most important. Coupled with the realization that budgetary constraints require a multi-year plan to ensure adequate fire protection features are provided to the NIH, this document defines a prioritized program to encompass FY 93-94-95-96 funding to accomplish the goal of a fire-safe physical plant. The Division of Engineering Services (DES) has already accomplished much of the preliminary planning through various studies and projects over the last five years, and they will be referenced in this document as appropriate. Additional projects are presently underway (i.e., the Campus Water Distribution System Study) which may also impact the *NIH Fire Protection Master Plan*; therefore the DES will have to coordinate the results from these studies into this Master Plan.

FY 93 FUNDING

- Conduct a life safety survey and analysis of NIH campus facilities.

  Contract a reputable fire protection engineering consultant to conduct a fire/life safety survey and analysis of all on-campus NIH buildings

(excluding the Building 10 Complex) to identify fire-safety deficiencies, develop a prioritized list of recommendations for correcting those deficiencies and provide DES the necessary cost estimates for incorporating into future budget documents. This would be an analogous study to the *Life Safety Survey and Analysis - Building 10 Complex* which was completed in August 1992. Based on this previous study and the approximate square footage involved, it is estimated that a full-campus analysis will cost the DES under $150,000. The DES has an open-end fire protection task order contract which can be utilized to fund this initiative in FY 93. Furthermore, the Chief, Fire Prevention Section (FPS), EMB, can serve as co-Project Officer and/or technical advisor for the project. The EMB strongly recommends that this mechanism be utilized and that the study proceed expeditiously.

- Correct the Priority 1 Deficiencies as defined in the *Life Safety Survey and Analysis - Building 10 Complex.*

  In 1992, a fire protection engineering consulting firm was contracted to survey the Building 10 Complex and develop a report outlining prioritized life safety deficiencies and recommendations for corrective action. The Chief, Team 1, DCB/DES and the Chief, FPS/EMB served as co-Project Officers for this project. Life safety deficiencies were noted as "Building Wide" and "Specific Area" in priority order, with "Priority 1" being the most critical type of deficiency. Examples of Priority 1 deficiencies are the lack or inadequacy of two hour fire separation walls for designated Areas of Refuge and the lack or inadequacy of two hour fire rated separation walls between the Health Care Occupancies (patient care units) and other occupancies. Corrective actions required to abate "Building Wide Priority 1" deficiencies are of a magnitude which will require the services of a qualified A/E firm for the development of plans and specifications.

  Cost estimates for correcting these deficiencies were provided by the contractor but will need to be adjusted for inflation and any asbestos abatement which may be necessary.

FY 94 FUNDING

- Design and install a new NIH campus-wide fire alarm reporting system to replace the existing "loop" which connects the individual building fire alarm systems to the NIH Fire Department.

In December 1992 a "Master Plan" was developed by a fire protection engineering consulting firm, contracted by DES, for the installation of a new standardized campus-wide fire alarm reporting system which connects the individual building fire alarm systems to the NIH Fire Department. This document was reviewed by the EMB who concurred with the recommendations. The existing campus-wide fire alarm reporting system is woefully antiquated and only marginally reliable. If this system fails, the fire alarm systems in the majority of buildings on campus will not be connected to the NIH Fire Department; therefore, activated alarm devices in the buildings will not be transmitted to the NIH firefighters.

Most of the deficiencies in the system are age related. Spare parts are not readily available and, in many cases, are no longer manufactured. Additionally, because of the age and condition of the fire alarm reporting trunk line, maintenance is difficult to accomplish.

The installation of state-of-the-art fire alarm systems in the newer facilities, specifically Buildings 29B, 49 and the William H. Natcher Building, warrant the installation of a reliable state-of-the-art campus-wide fire alarm reporting system.

It is estimated that this project will have a construction cost of approximately $2,150,000 based on the DES study; however, this figure will have to be adjusted for inflation and for any asbestos abatement which may be required. Design should be completed in FY 94 with construction to follow in FY 95.

- Design and install fire alarm reporting and fire suppression systems to correct deficiencies at the NIH Animal Center (NIHAC) in Poolesville.

  In September 1990 a fire protection engineering consulting firm, contracted by DES, surveyed the NIHAC and developed a report outlining fire suppression and fire alarm reporting system related deficiencies at the facility. This study was reviewed by the EMB and it was agreed that the recommendations for corrective action should be adopted.

  Specific concerns addressed in the study were the availability of water for manual firefighting operations, an antiquated and non-expandable fire alarm reporting system and the lack of complete automatic sprinkler protection for the facility.

Construction at the NIHAC is anticipated to increase and design analysis studies currently indicate the existing NIHAC fire alarm reporting system has no capability for expansion. Additionally, replacement parts for the fire alarm reporting system are difficult to obtain due to the antiquated nature of the system.

Sprinkler system installations at the NIHAC are typically requested at the POR stage; however, due to limited funding, all occupied facilities are not provided with full automatic sprinkler protection. The installation of automatic sprinkler protection for buildings at the NIHAC is crucial from both a structural and life safety standpoint since response times by the fire department may be as long as 20 to 30 minutes.

Based on the 1990 study it is estimated that this project will have a construction cost of approximately $180,000; however, this figure will have to be adjusted for inflation and modified to include any asbestos abatement which may be required. The design of this project should be completed in FY 94 with construction to follow in FY 95.

- Install new individual building fire alarm systems and automatic sprinkler protection in Buildings 29, 29A, 30, 36 and 37, and correct other fire/life safety deficiencies as identified in the *Life Safety Survey and Analysis* requested for funding in FY 93.

  These large laboratory buildings were selected for FY 94 funding because of the increased risk to both life and property due to the volumes of flammable liquids utilized, the fact that animals are housed in these facilities and the impact to the mission of the NIH which would be realized by the loss of research capabilities subsequent to a major fire. Because of the large volumes of flammable liquids stored in many individual laboratories at the NIH, the National Fire Protection Association (NFPA) would actually categorize them as "flammable liquid storage rooms" rather than "laboratories."

  The cost of implementing this project would be determined as a result of the FY 93 *Life Safety Survey and Analysis*; however, a very rough estimate, to be used only for *preliminary* planning purposes would be between $300,000 and $350,000 per building. This estimate is based upon the size of the buildings and the anticipated level of effort required to install the systems; however, it does not include any asbestos abatement which may be necessary.

- Correct deficiencies in fire protection systems which are identified in the DES Campus Water Distribution System Study.

  Currently, the Special Projects Office, DES has contracted the services of an A/E firm to perform a study of the campus water distribution system to examine the effect on system pressure due to the installation of backflow preventers as required by Washington Suburban Sanitary Commission (WSSC).

  From a fire protection standpoint, a 10 psi drop in water pressure is a serious concern. Since automatic sprinkler systems require a minimum working pressure to operate, the installation of fire pumps may be necessary in areas where the water pressure has been identified as marginal. To compound the problem, buildings currently provided with fire pumps may require new fire pumps sized for the 10 psi drop in campus pressure. Therefore, a boosting mechanism for the campus water pressure must be identified and implemented to offset these anticipated problems.

  The study of the campus water distribution system is a part of the Master Utility Plan and is assigned Work Request Number 003437. The Special Projects Office, in conjunction with WSSC, is investigating options for supplementing the campus water pressure to offset the estimated 10 psi pressure loss associated with the installation of the backflow preventers.

FY 95 FUNDING

- Correct remaining deficiencies (Priority 2 and 3) identified in the *Life Safety Survey and Analysis - Building 10 Complex.*

  In 1992, a fire protection engineering consulting firm was contracted to survey the Building 10 Complex and develop a report outlining prioritized life safety deficiencies and recommendations for corrective action. Life safety deficiencies were noted as "Building Wide" and "Specific Area" in descending priority levels. "Priority 1" deficiencies are recommended for abatement in FY 93. Priority 2 and 3 deficiencies are less critical to life safety but require correction to ensure compliance with the National Fire Codes, the BOCA National Building Code and Joint Commission of Accreditation of Healthcare Organizations (JCAHO) requirements.

Cost estimates for correcting these deficiencies were provided by the contractor but will need to be adjusted for inflation and any asbestos abatement which may be necessary.

- Install new individual building fire alarm systems and automatic sprinkler protection in Buildings 3, 6, 6A, 7, 9, and the 14-Group, and correct other fire/life safety deficiencies as identified in the *Life Safety Survey and Analysis* requested for funding in FY 93.

  These laboratory buildings were selected for FY 95 funding because of the increased risk to both life and property due to the volumes of flammable liquids utilized, the fact that animals are housed in these facilities and the impact to the mission of the NIH which would be realized by the loss of research capabilities subsequent to a major fire. Because of the large volumes of flammable liquids stored in many individual laboratories at the NIH, the National Fire Protection Association (NFPA) would actually categorize them as "flammable liquid storage rooms" rather than "laboratories."

  The cost of implementing this project would be determined as a result of the FY 93 *Life Safety Survey and Analysis*; however, a very rough estimate, to be used only for *preliminary* planning purposes would be between $250,000 and $300,000 per building. This estimate is based upon the size of the buildings and the anticipated level of effort required to install the systems; however, it does not include any asbestos abatement which may be necessary.

FY 96 FUNDING

- Install new individual building fire alarm systems and automatic sprinkler protection in Buildings 20, 16, 1, 31 A/B/C, 13, 11, and 35, and correct other fire/life safety deficiencies as identified in the *Life Safety Survey and Analysis* requested for funding in FY 93.

  These buildings were selected because of the increased risk involved in dormitory occupancies, the historical nature of the Stone House and the "mission importance" to the NIH of the administrative buildings and the research support facilities.

  The cost of implementing this project would be determined as a result of the FY 93 *Life Safety Survey and Analysis*; however, a very rough estimate, to be used only for *preliminary* planning purposes would be between $200,000 and $250,000 per building except for the Building 31

complex which would total approximately $500,000 - $600,000 for all three buildings (A, B and C). Estimates are based upon the size of the buildings and the anticipated level of effort required to install the systems; however they do not include any asbestos abatement which may be necessary.

NIH FIRE PROTECTION MASTER PLAN

A PROGRAM FOR CORRECTING FIRE AND LIFE SAFETY DEFICIENCIES ON THE NIH CAMPUS AND THE NIHAC

SUMMARY

(projects are listed in priority order by fiscal year)

FY 93 FUNDING

- Conduct a life safety survey and analysis of the NIH campus facilities.
- Correct Priority 1 Deficiencies as defined in the *Life Safety Survey and Analysis - Building 10 Complex.*

FY 94 FUNDING

- Design new campus-wide fire alarm reporting system.*
- Design project to correct fire alarm reporting and fire suppression deficiencies at the NIH Animal Center (NIHAC) in Poolesville.*
- Install new individual building fire alarm systems and automatic sprinkler protection in Buildings 29, 29A, 30, 36 and 37, and correct other life safety deficiencies in these facilities.
- Correct deficiencies in fire protection systems identified in the *DES Campus Water Distribution Study.*

FY 95 FUNDING

- Construct new campus-wide fire alarm reporting system.*
- Install new systems to correct fire alarm reporting and fire suppression deficiencies at the NIHAC.*
- Correct remaining deficiencies (Priority 2 & 3) identified in the *Life Safety Survey and Analysis - Building 10 Complex.*
- Install new individual building fire alarm systems and automatic sprinkler protection in Buildings 3, 6, 6A, 7, 9, and the 14-Group, and correct other life safety deficiencies in these facilities.

FY 96 FUNDING

- Install new individual building fire alarm systems and automatic sprinkler protection in Buildings 20, 16, 1, 31 A/B/C, 13, 11, and 35, and correct other life safety deficiencies in these facilities.

* Both projects equally share the highest priority for the budget year identified.

TUESDAY, APRIL 9, 2002.

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. RUTH L. KIRSCHSTEIN, DIRECTOR
DR. STEPHEN KATZ, DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES
DR. STEPHEN STRAUS, DIRECTOR, NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE
DR. DUANE ALEXANDER, DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
DR. DONNA DEAN, ACTING DIRECTOR, NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING
DR. JOHN RUFFIN, DIRECTOR, NATIONAL CENTER ON MINORITY HEALTH AND HEALTH DISPARITIES
DR. GERALD KEUSCH, DIRECTOR, FOGARTY INTERNATIONAL CENTER
KERRY WEEMS, ACTING DEPUTY ASSISTANT SECRETARY FOR BUDGET, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. REGULA. We will get the hearing started today.

We are happy to welcome you, Dr. Kirschstein. Welcome again and again and again. Always happy to see you here with your team. So I will let you sort of manage the witnesses as you see the way that would be the most productive, and you can introduce them as we go.

OPENING REMARKS—DR. KIRSCHSTEIN

Dr. KIRSCHSTEIN. Thank you, Mr. Chairman—Mr. Chairman, Mr. Obey. We are pleased to continue the fiscal year 2003 appropriations hearings for NIH and expand on the two previous presentations.

Today's presentations will discuss the various collaborations that are so important to modern-day biomedical research, which are far more complex, covering many more disciplines scientifically, and require broader interactions than ever before. These collaborations are among the various Institutes and Centers of NIH, between NIH and other agencies within the Department of Health and Human Services, with other agencies of the Federal Government, with industry, with private foundations and with philanthropic organizations and between NIH staff and patients and patients' advocates and all combinations of the above.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Statement of the Acting Director, Dr. Ruth L. Kirschstein, to the House Appropriations Subcommittee on Labor-HHS-Education
April 9, 2002

on Collaborations in Biomedical Research
accompanied by

Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases
Dr. Stephen Straus, Director, National Center for Complementary and Alternative Medicine
Dr. Duane Alexander, Director, National Institute of Child Health and Human Development
Dr. Donna Dean, Acting Director, National Institute of Biomedical Imaging and Bioengineering
Dr. John Ruffin, Director, National Center on Minority Health and Health Disparities
Dr. Gerald Keusch, Director, Fogarty International Center
Mr. Kerry Weems, Acting Deputy Assistant Secretary for Budget, DHHS

Opening Statement of Dr. Ruth Kirschstein, Acting Director, NIH

COLLABORATIONS IN BIOMEDICAL RESEARCH

Mr. Chairman, Members of the Committee,

We are pleased to continue the FY 2003 appropriations hearings for NIH and expand on the two previous presentations. Today's presentations will discuss the various collaborations that are so important to modern day biomedical research which is far more complex, covers many more scientific disciplines and requires broader interactions than ever before. These collaborations are among the various Institutes and Centers of NIH; between NIH and other agencies within the Department of Health and Human Services; with other agencies of the Federal Government; with industry; with private foundations and with philanthropic organizations; between NIH staff and patients; and patient advocates and all combinations of the above.

Again, it is clear that each of the Institutes and Centers has developed such collaborations to fulfill its mission.

The National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS) and the National Institute on Aging (NIA), along with the Office of Research on Women's Health (ORWH), the National Center on Minority Health and Health Disparities (NCMHD), the National Center for Complementary and Alternative Medicine (NCCAM), and the National Institute of Dental and Craniofacial Research (NIDCR) have partnered with other Federal agencies and four pharmaceutical companies to support the newly launched Osteoarthritis Initiative. This public-private partnership will develop clinical research resources that support discovery and evaluation of biomarkers and surrogate endpoints for clinical trials on osteoarthritis.

Patients with cancer are among the most frequent users of complementary and alternative medicine. The National Center for Complementary and Alternative Medicine (NCCAM) in collaboration with the National Cancer Institute (NCI) is supporting studies to determine whether these practices truly benefit patients with cancer. They include the large clinical trial of the use of selenium and vitamin E to prevent the development of cancer. In addition, NCCAM and the National Heart, Lung and Blood Institute (NHLBI), the National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke (NINDS) are supporting the largest study ever conducted of an herbal medicine, ginkgo biloba in preventing dementia in the elderly.

The National Institute of Child Health and Human Development (NICHD) leads a trans-agency initiative on Early Learning and School Readiness. This program evaluates the effectiveness of different models of early childhood education that consider both cognitive and social development. The studies are supported by NICHD, the National Institute of Mental Health (NIMH), the Administration for Children and Families of the Department of Health and Human Services (ACF, DHHS), the National Science Foundation (NSF) and the Department of

Education and will also develop and evaluate curricula for children "at risk of failure to learn to read and do mathematics."

The existence of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) is rooted in collaborations between, and among, in particular, the NHLBI, NCI, the National Center for Research Resources (NCRR), and the National Institute of General Medical Sciences (NIGMS), as well as with the NSF and the Department of Energy. Innovative Science areas include:

1. Biomaterials – To treat injuries and diseases of the nervous system, biomaterials are used to create scaffolding that will provide a platform for nerve cells and fibers to grow enabling the reconstruction of damaged and diseased neural pathways.

2. Biosensors – The electronic tongue is an array of hundreds of chemical microsensors on a silicon wafer that will identify individual substances within a mixture instantaneously. Applications for this technology include drug dosage, drug metabolism, blood sugar, cholesterol content and medical diagnostics.

The National Center for Minority Health and Health Disparities works collaboratively with the other NIH Institutes and Centers on a variety of projects. For instance, the Center builds research infrastructure and capacity at dental schools that train minority dentists and conducts collaborative research aimed at reducing the disparity in oral health in minority and rural populations. The Center also conducts research to evaluate potential interventions to help patients and medical communities to overcome the barriers that inhibit adherence to treatment regimens among racial and ethnic minorities and those who live in poverty.

In no area are collaborations more important than in the NIH international research portfolio. This involves the Fogarty International Center and all the institutes and centers, as well as HHS and other governmental agencies, academic centers in the U.S., international organizations, and scientists and institutions in foreign countries. There are many examples of international research, including training in behavioral and prevention research on HIV/AIDS, now extending to the care of sick patients, adults and children, particularly in developing countries; preserving biodiversity while responsibly prospecting for new therapeutic compounds from natural products in fragile ecosystems in the tropics; and the Minority International Research Training Program, which provides an international research training opportunity for young minority undergraduate and graduate medical and science students to work abroad in a mentored environment.

With me today are:

- Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

- Dr. Stephen Straus, Director, National Center for Complementary and Alternative Medicine (NCCAM)

- Dr. Duane Alexander, Director, National Institute of Child Health and Human Development (NICHD)
- Dr. Donna Dean, Acting Director, National Institute of Biomedical Imaging and Bioengineering (NIBIB)
- Dr. John Ruffin, Director, National Center on Minority Health and Health Disparities (NCMHD)
- Dr. Gerald Keusch, Director, Fogarty International Center (FIC)

Dr. KIRSCHSTEIN. Again, it is clear that each of the Institutes and Centers have developed such collaborations to fulfill its mission and you will hear about some of them today. The panel members to my immediate left, are Dr. Donna Dean, the Acting Director of the new National Institute of Biomedical Imaging and Bioengineering; Dr. Stephen Katz, Director of Arthritis and Musculoskeletal and Skin Diseases; Dr. Stephen Straus, Director of the National Center for Complementary and Alternative Medicine; and Dr. Duane Alexander, Director of the National Institute of Child Health and Human Development.

To my immediate right, Dr. John Ruffin, the Director of the National Center on Minority Health and Health Disparities; Dr. Gerald Keusch, Director of the Fogarty International Center; and as always, we are delighted to have Mr. Weems with us.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Mr. REGULA. Alternative medicine, what is alternative medicine?

Dr. KIRSCHSTEIN. I am going to let Dr. Straus answer that for you.

Dr. STRAUS. Complementary and alternative medicine involves diverse health care modalities that are unproven scientifically—chiropractic, massage, herbal medicines, acupuncture and the like—and I will be happy to speak more about those in time.

Mr. REGULA. I just wanted you to clarify it.

Dr. KIRSCHSTEIN. We will start with Dr. Katz.

OSTEOARTHRITIS

Dr. KATZ. It is an honor to be here to represent the National Institute of Arthritis and Musculoskeletal and Skin Diseases. We have a number of very effective collaborations in which the American people benefit.

The focus today is on the newly launched osteoarthritis initiative. Let me put it in the context of the importance of osteoarthritis. It is the most common form of arthritis and affects more than 20 million people currently; and the incidence will increase as the number of older people in the United States increases.

Osteoarthritis results from a wearing away of cartilage. Cartilage is the cushion that sits on the ends of our bones so that when bones come together either in the elbows or the knees or the hip or the fingers or the ankle in some peoples' cases, and that cushion doesn't work, it is due to the wearing away of that cushion. We know what has come to be called osteoarthritis is probably due to many, many different causes, and we know that osteoarthritis is the most common form of arthritis in the world.

Currently, there are no treatments to modify the disease. We can offer only analgesics, pain medications, some alternative therapies, some physical therapy and ultimately, when it becomes totally disabling, we can offer total joint replacement, which is a commonly used procedure these days.

OSTEOARTHRITIS INITIATIVE

After a number of scientific meetings, we concluded there was a clear need to identify and develop surrogate markers for disease

progression in osteoarthritis. This was the basis for the osteoarthritis initiative, which is a public-private partnership.

This initiative requires the enrollment of a large cohort of individuals who would be studied over a long period of time, a long enough period of time so that they will develop the disease. The analysis will be of serum, as well as DNA, as well as images from MRIs that are going to be done over the course of the study, which is approximately seven years.

Now, I brought three posters along to illustrate the collaborations in this initiative. The first poster illustrates the structure of the consortium. On the right, you can see that there are six centers or institutes that are involved from NIH. Each of these centers or institutes has a particular interest in osteoarthritis. The leaders of this consortium are the NIAMS and the National Institute on Aging. The industrial partners are shown on the left.

The NIH Foundation is utilized in order to take the dollars from industry and put them into this partnership. As well, the FDA, as an important partner in this, serves as a liaison to this consortium. We also have a steering committee with a project officer and contracting officer, and this is the outline of the structure of the consortium.

The second poster illustrates how financial resources will be managed in this consortium. Money from industry goes into the NIH Foundation, and then that is commingled with the money from the NIH institutes and centers, and all of that money goes into contracts to support a data coordinating center as well as the clinical sites that will accrue the study patients. There will be four to six clinical sites in order to follow these 5,000 individuals during the course of this study.

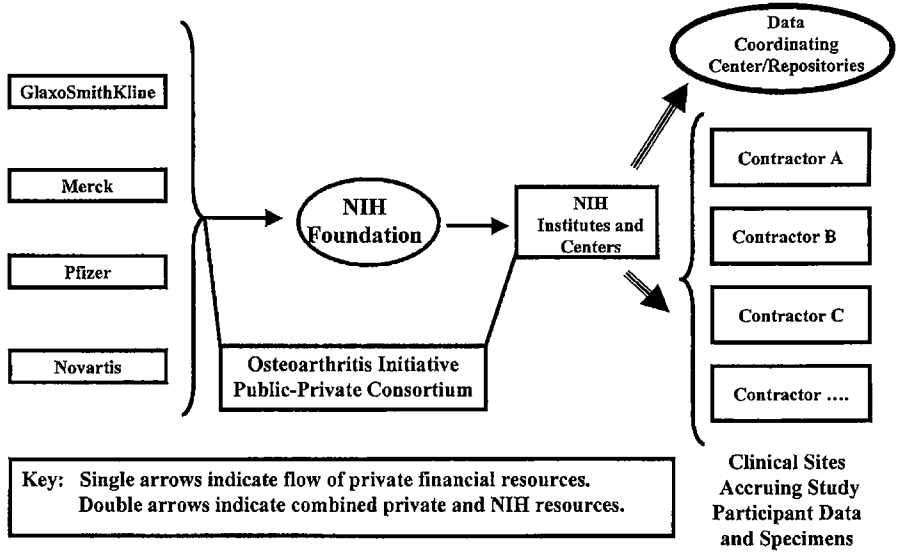
If I could have the last of the posters, that shows how data and specimens will be managed. The data and specimens will all be sent to the data coordinating center, which will be the repository. This material and the information from the imaging will then go back to the NIH institutes and centers. A most important element of this partnership is the immediate public access to all of the materials. There is no special access by any of the partners, either industrial partners or NIH partners. Everyone will have access according to a review process, so that the partners, as well as all of pharma, as well as all of the bioengineering companies, as well as academics, academic institutions around the country, as well as the intramural research program will all have access to this material. This process will form the basis for information sharing so that all of this material becomes available very, very quickly to everyone.

[The information follows:]

Osteoarthritis Initiative Consortium
NIAMS
NIA
NIDCR
NCCAM
ORWH
NCMHD
NIH FOUNDATION
NIH PARTNERS
PHARMA PARTNERS
STEERING COMMITTEE
FDA LIAISON
GlaxoSmith Kline, Merck, Novartis, Pfizer
CONTRACTING OFFICER
PROJECT OFFICER
OSMB
NIH DIRECTORS NIAMS, NIA

Osteoarthritis Initiative Project Model

Financial Resource Management



Osteoarthritis Initiative Project Model

Management of Data and Specimens

We anticipate that the initiative can speed progress towards identifying risk factors, the development of better markers for the disease and its progression and, ultimately, better treatments and preventive measures.

In summary, the initiative represents significant investments of time, energy and financial resources; and we are very excited about the promise it offers for advancing medical research and improving public health, which are the goals of the NIH.

I would be happy to answer any questions about this or anything else later on.

Dr. KIRSCHSTEIN. The next speaker will be Stephen Straus, the National Center for Complementary and Alternative Medicine, who has already started to give you the definition.

OPENING REMARKS—NCCAM

Dr. STRAUS. Thank you, Mr. Chairman and Mr. Obey. It is a privilege to join my NIH colleagues and research partners and talk to you about collaboration.

NCCAM, the national center for complementary and alternative medicine, by funding rigorous research, determines which CAM—complementary and alternative medicine—practices are safe and effective and why. These are highly popular modalities that millions of Americans are using despite the fact they are unproven. CAM claims to benefit or prevent countless health conditions across the entire lifespan, addressing virtually all disciplines of medicine.

For NCCAM, then, collaboration is not just a means of leveraging our funding; it is a necessity to enrich our scientific understanding and outreach to address all the important challenges of complementary and alternative medicine.

If I can begin with this poster to your right, let me point out that our research enterprise from basic early studies and clinical trials to the dissemination of information to scientists, practitioners and the general public is a process that is driven, enhanced and informed by input from many individuals: investigators, the general public, from members of our national advisory council, and members of the transagency CAM coordinating committee, which I chair, and which includes representatives of over 30 NIH institutes, centers and offices and other health agencies in the Federal Government.

Collaboration of this type enhances our productivity throughout. I am going to illustrate our collaborations in a way that I would with all of our colleagues.

NCCAM AND NCI COLLABORATION

We collaborate with most of the institutes and centers by highlighting the example of the National Cancer Institute. Our collaboration with NCI is based on the fact that most patients with cancer, particularly as their disease progresses, turn to complementary alternative practices to sustain the quality and dignity of their life, to improve their last months on Earth and to afford them some relief from the discomfort of their disease and its treatment. With the NCI, we are supporting basic research and large clinical trials.

An example of basic research is a study in the laboratory of breast cancer, where we are looking at the interaction of the important hormonal drug that breast cancer patients take known as Tamoxifen with soybean phytochemicals. Soy contains hormonal-like chemicals that women often take to relieve the side effects of menopausal change, including side effects caused by Tamoxifen. We are mounting such a study today with the NCI.

With the NCI, as well, we are mounting two of the largest CAM studies ever conducted rigorous, Phase III multicenter trials. The first is a study of shark cartilage as adjunctive therapy in 570 men with inoperable non-small-cell lung cancer. The second trial is testing Vitamin E and selenium to prevent prostate cancer, a study involving 32,000 American men oversampling for African American men in whom prostate cancer has a greater burden of disease. Those are examples of basic and clinical projects that NCCAM supports.

Our studies also require collaborations with industry and, particularly, small businesses, because the American consumer can't access highly standardized, high quality herbal and chemical products. We work with industry to manufacture them so they meet our standards, so that our research findings will hopefully be replicable and generalizable to the American public. The end result of our research from basic to clinical is information that flows to the public and the practitioners.

NCCAM'S INFORMATION-DISSEMINATION ACTIVITIES

In this regard, we partnered with the National Library of Medicine over a year ago to mount a Web-based system, known as CAM on PubMed, which puts at the fingertips of every American with a computer at home or in their public libraries, over a quarter of million articles related to this field from 70 countries in 45 different languages.

In addition, we have a toll-free clearinghouse in English and Spanish, fact sheets newsletters and town meetings. We reach out to the entire United States, rural and urban to communicate our findings.

NCCAM CLINICAL TRIALS

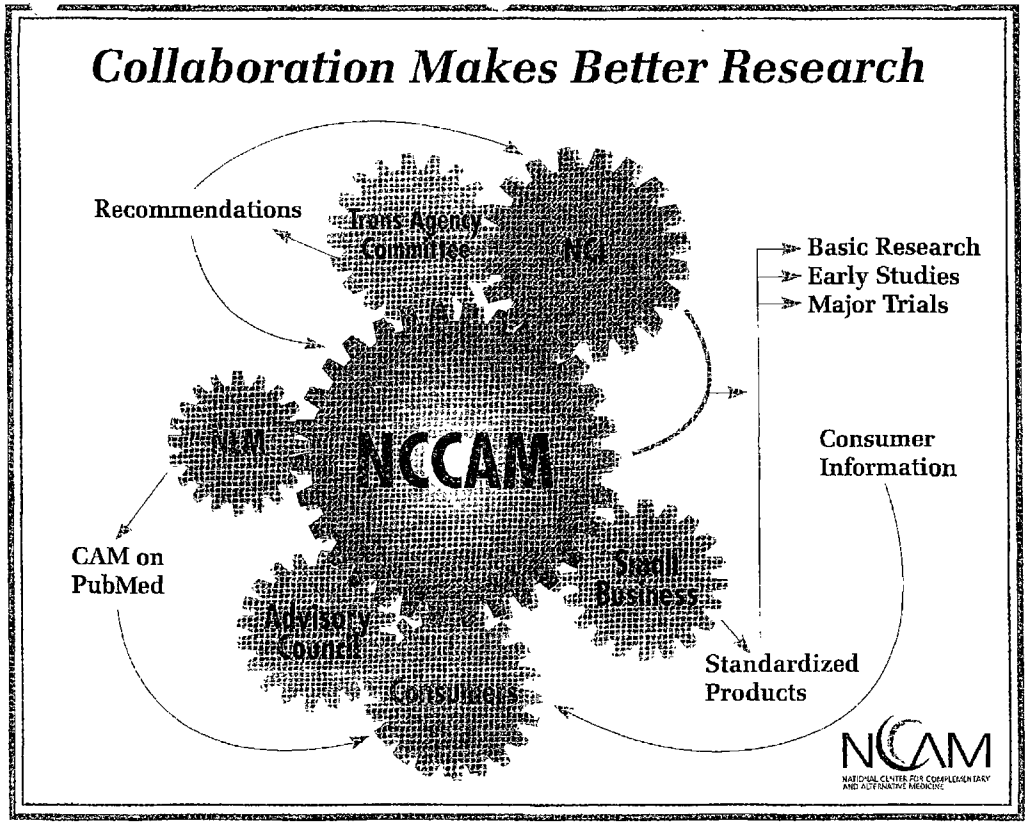
If I could have the final poster, the capping result of our research enterprise is the large clinical trials, and I mentioned two with regards to the National Cancer Institute, but we are privileged to work with the Aging, Heart, Lung, Blood and Neurology Institutes in the largest study of a herbal medicine, ginkgo biloba, for prevention of Alzheimer's disease.

With Dr. Katz and his colleagues in the Arthritis Institute, we are supporting two large studies of alternative practices for osteoarthritis, the very disorder that he discussed a moment ago, one involving acupuncture and one involving glucosamine and chondroitin. Similarly, we have studies with the National Institute of Mental Health, the National Heart Institute, Diabetes Institute and many others.

Mr. Chairman, collaboration is essential for NCCAM. It is a large part of what we do, and I believe a large part of why we are begin-

ning to succeed. I am very happy to take your questions on this and related issues later. Thank you.

[The information follows:]


Collaboration Makes Better Research
Recommendations
Trans-Agency Committee
NCI
Basic Research
Early Studies
Major Trials
NIH
NCCAM
Consumer Information
CAM on PubMed
Small Business
Advisory Council
Consumers
Standardized Products
NCAM
NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

NCCAM Phase III Randomized Controlled Clinical Trials

Condition	Therapy	Cosponsor
Dementia	*Ginkgo biloba*	NIA, NHLBI, NINDS
Osteoarthritis	Acupuncture	NIAMS
Osteoarthritis	Glucosamine/chondroitin	NIAMS
Lung cancer	Shark cartilage	NCI
Prostate cancer	Vitamin E/selenium	NCI
Minor depression	St. John's wort	NIMH, ODS
Coronary artery disease	EDTA chelation therapy	NHLBI
Benign prostate hypertrophy	Saw palmetto/African plum	NIDDK, ODS

NCCAM
NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

OPENING REMARKS—NICHD

Dr. KIRSCHSTEIN. Dr. Duane Alexander, the Director of the National Institute of Child Health and Human Development.

Dr. ALEXANDER. Mr. Chairman, Mr. Obey, the extensive collaborations of the NICHD and other NIH institutes and centers that are the focus of today's hearing are undertaken for a variety of reasons.

MATERNAL FETAL MEDICINE UNITS

Collaborations in research often take advantage of a specific resource that one institute has that fills a purpose of another institute. For example, NICHD maintains a network of maternal fetal medicine units that comprises 14 sites to conduct cooperative clinical trials in obstetrics. Their purpose is to design trials with a common protocol used at each site to study ways to improve pregnancy outcome, and quickly recruit a large enough number of patients to get a clear answer rapidly.

The Neurology Institute and the Heart-Lung Institute, rather than start up similar networks for their own perinatal studies, are partnering with the NICHD network to do these studies. Doing it this way saves time, money and staff resources.

On a given topic, we may collaborate with many different institutes. Women's health is one example. We work collaboratively with the Infectious Diseases Institute in research on topical microbicides to prevent HIV transmission; with the Diabetes and Kidney Institute, on urogynecology and incontinence; with the Dental and Arthritis Institutes, on osteoporosis prevention; with the Cancer and Heart Institutes, on contraceptives in relation to cancer and cardiovascular disease; with the Fogarty Center on international reproductive research and training; and with Minority Health and Women's Health, on supporting women's reproductive health centers.

LONGITUDINAL ENVIRONMENTAL HEALTH STUDY

Sometimes Congress specifically asks us to work collaboratively. For example, in the largest collaborative activity of all, Congress in the year 2000 asked NICHD to lead a consortium of Federal agencies in developing a longitudinal study of environmental influences on children's health and development. The Environmental Health Sciences Institute at NIH, the Centers for Disease Control and the Environmental Protection Agency have joined NICHD in leading a consortium of 22 NIH institutes, 11 DHHS agencies and nine departments in planning and designing this study.

BACK-TO-SLEEP CAMPAIGN

Different types of collaboration are used when we try to translate research findings to practice. For example, this graph that you see documents the constancy of the rate of sudden infant death syndrome deaths before research revealed that a back-sleeping position reduced SIDS risk, and then the reduction by half in the SIDS rate since the NICHD-led "Back-to-Sleep" campaign began in 1994.

Our initial major collaborators in the public information campaign were the Maternal and Child Health Bureau, the American

Academy of Pediatrics and the SIDS Alliance. To broaden the message, we enlisted the support of industry. Gerber put the message on six million boxes of baby cereal; and Pampers put the "Back-to-Sleep" message on all of their infant baby diapers. You can't miss this message. It is in three languages—French, Spanish, as well as English.

To reach the African American community more effectively, the Minority Health Center helped us join with the National Black Child Development Institute in designing culturally appropriate materials and outreach methods.

This collaborative campaign made it possible for the Department of Health and Human Services to reach its goal of reducing infant mortality in the country to below seven deaths per thousand live births by the year 2000. Substantial portions of our 2003 budget request will continue and enhance these collaborative studies.

Thank you.

Dr. KIRSCHSTEIN. Dr. Donna Dean, the Acting Director of the National Institute of Biomedical Imaging and Bioengineering.

OPENING REMARKS—NIBIB

Dr. DEAN. Thank you. Good afternoon, Mr. Chairman, Mr. Obey and Mr. Sherwood. As the Acting Director of the National Institute of Biomedical Imaging and Bioengineering, I am delighted to speak to you about collaborations that NIH is fostering as one of the two newest Institutes and Centers at the NIH.

COLLABORATIVE OPPORTUNITIES

A little over a year ago, the Congress noted that a number of Federal departments and agencies support imaging and engineering research with potential medical applications, but felt that a central body was needed to lead these efforts. NIBIB was created to fill this role to support research in areas that cross disciplines, science areas, diseases and organ systems.

The very existence of NIBIB is rooted in collaboration, bringing together scientists working in multiple disciplines from multiple agencies and working to develop innovative technologies in biomedical imaging and bioengineering.

I brought to you today two examples to show you the work we are supporting. These projects were initially funded by existing NIH Institutes and Centers and were subsequently transferred to NIBIB as they are exemplary of our mission.

The first poster shows one of our bioengineering projects, microfabricated microneedles for drug delivery, originally funded by the National Institute of General Medical Sciences and transferred to NIBIB this year. The left side of the poster illustrates the size of the microneedles relative to the size of a finger. The right side of the poster is a magnified view of the needles that are used to deliver a drug, such as insulin for diabetes. Because the needles are long enough to penetrate the skin, but short enough to avoid hitting nerves the patient feels no pain.

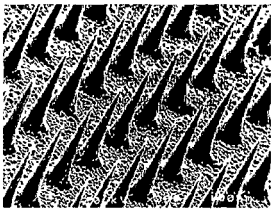
[The information follows:]

Microfabricated Microneedles for Drug Delivery (8-R01-EB00260-03)

Principal Investigator: **Mark Prausnitz,** Georgia Institute of Technology



Size of experimental microneedle array is shown by its placement on the researcher's finger. There are 400 needles in the array.



Electron micrograph close-up of the needles, with added color.

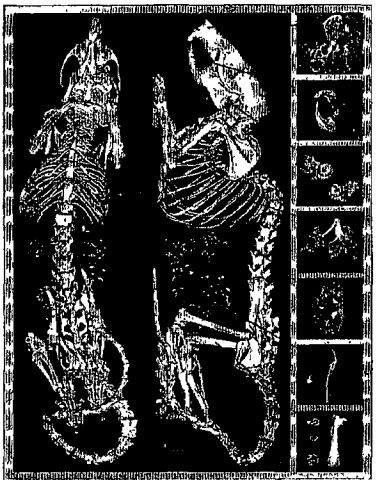
Source: Photographs are copyrighted by the Georgia Tech Research Corporation and may be freely used by the news media with credit to the Georgia Institute of Technology. The photographer is Stanley Leary, Georgia Tech Communications Division.

Dr. DEAN. The second poster shows images from a newly developed micro CT scanner, an NIBIB biomedical imaging project originally funded by the National Center for Research Resources and transferred to us in this fiscal year. Along the right side of the poster, high resolution images showing the microarchitecture of a living animal are seen. Tiny structures, such as the middle ear, which is the third picture down on the right, are shown in minute detail. These scanners will enable researchers to observe diseased states in small live animals and, it is hoped, develop technologies that can then later be translated into imaging technologies for use in humans.

[The information follows:]

Multidisciplinary Micro CT-3D Imaging Facility (8-R01-EB00305-06)

Principal Investigator: **Erik Ritman,** Mayo Clinic



Source: Copyright © 1996-2002 Mayo Foundation for Medical Education and Research.

NEW RESEARCH INITIATIVES

Dr. DEAN. I am proud to announce that yesterday NIBIB announced that we awarded our first new competing research project grant. Other NIH Institutes and Centers have worked in a foster parent role with us over the past few months to assist us in shepherding applications through the Peer Review and Secondary Institute Council review process. Our first grant, a Bioengineering Research Partnership (BRP) awarded to Yale University, brings together six academic partners and one industrial partner to develop high resolution functional MRI and MR spectroscopy at high field strength. This grant, as well as others we will be awarding in the next few weeks, reflects research that brings together several disciplines.

These exciting projects that I have highlighted today are a few examples of the types of scientific challenges that provide rich opportunities for NIBIB research. After only one year, we are making substantial progress in translating the vision that Congress had for NIBIB into the reality of a forward-looking research Institute.

I am pleased to respond to any of the questions from the committee later.

Dr. KIRSCHSTEIN. Dr. John Ruffin, the Director of the National Center on Minority Health and Health Disparities.

OPENING REMARKS—NCMHD

Dr. RUFFIN. Mr. Chairman and members of the committee, I am very pleased to be here today to testify on the subject of collaboration. This is a topic that goes to the heart of how we operate.

I am honored to be here with my distinguished colleagues from the National Institutes of Health. As we are far from eliminating health disparities, it is imperative that we continue to work together to address health matters that disproportionately affect racial and ethnic minorities and the medically underserved.

As you can see from poster one, Congress mandated that the NCMHD serve as the focal point for planning and coordinating minority health and other health disparity research across the National Institutes of Health. The NCMHD programs are aimed at addressing gaps in health disparities research and training. We focus on inclusive or targeted research domains or training programs relevant to the health of minority or medically underserved populations.

I am pleased to report that over the years, the NCMHD or its predecessor, the Office of Research on Minority Health, has collaborated with every NIH Institutes and Centers on minority health or health disparity research study or training programs. Last year, Mr. Chairman, we were involved in 214 collaborations with the other NIHICs, the HHS Office of Minority Health and the Agency for Health Care Research and Quality.

I would like to use poster two to cite a few examples of our approach to collaborations. Just this past Friday, the American Academy of Ophthalmology released a very important study showing that glaucoma is the leading cause of blindness among a sample of Hispanic southern Arizona residents of Mexican descent, age 40 and over. The Proyecto VER program, which stands for vision eval-

uation and research project, was sponsored by the NCMHD and the National Eye Institute.

This was the first comprehensive study of vision loss and blindness among U.S. Hispanics. The study underscores the need for early detection of eye disease among Hispanic Americans. It also demonstrates the mutual benefits of collaboration: NEI obtained increased knowledge about eye disease and the NCMHD gained insight into an important disparity affecting the Hispanic population.

DIABETES PREVENTION PROGRAM

The NCMHD collaborated on two important studies with the National Institute of Diabetes and Digestive and Kidney Diseases. The first was the Diabetes Prevention Program which revealed that moderate diet and exercise could delay the onset of type 2 diabetes in overweight people. The second study with NIDDK is the minority organ and tissue donation program, which was designed to educate minorities on facts about organ and tissue transplantation. The study found that nationally supported, community-based programs can assist changing behavior impacting on a person's health, wellness norm and values.

JACKSON HEART STUDY

In partnership with the National Heart-Lung and Blood Institute, we are currently funding the Jackson Heart Study, whose participant enrollment is significantly increasing, with average of 50 participants a week; as of February 2000. A total of 1,441 participants have gone through the program since it started in September of 1999. The study evaluates the environmental and genetic factors influencing the development of cardiovascular disease in African American men and women.

HUMAN GENOME CENTER

With the National Human Genome Research Institute, we have established a human genome center at Howard University. The goals of the center are to improve the health status of African Americans through research on genome variation and to apply the knowledge to better understand the biomedical significance of gene-based differences.

The final poster illustrates some of the other collaborative work we are engaged in with some of the ICs that are present here at the table today. Dr. Alexander or I would be happy to discuss any of the child health projects in more detail with you. Dr. Keusch, who will present next, can also discuss our work with Fogarty on the Minority International Research Training program. Time permitting, I can also discuss what we are doing with the National Institute on Aging.

STRATEGIC PLAN

The NCMHD has worked with the NIH Director and other ICs to develop the NIH comprehensive strategic research plan and budget to reduce and ultimately eliminate health disparities. This plan will ensure a coordinated approach to addressing health disparities in the United States. We expect to continue collaborations

with the ICs and other Federal agencies on a variety of minority and health disparity issues.

Finally, I want to again thank you for inviting me here today to discuss NCMHD's work and plans for the future.

OPENING REMARKS—FIC

Dr. KIRSCHSTEIN. And last but not least, Dr. Gerald Keusch, the Director of the Fogarty International Center.

Dr. KEUSCH. Mr. Chairman, Mr. Obey, Mr. Sherwood, it is an honor to be here.

In fiscal year 2003, the Fogarty International Center will celebrate 35 years of international collaboration in biomedical research and research training. However, at no time in our history as a nation is this mission more relevant or more important. Disparities in health and resources result in tragically high infant and child mortality rates in developing countries, while in the past decade the life expectancy of adults throughout Africa has plummeted erasing the gains of the previous quarter century.

In a speech to the U.N. General Assembly in November 2001, President Bush recognized the inevitable consequences of the desperation and hopelessness that accompanies poverty and ill health, saying that we must offer an alternative of opportunity and hope. Biomedical research is an alternative of opportunity and hope.

As NIH conducts research to improve the health of Americans, we can also share our new knowledge and work to ensure that research addresses the critical global health needs that impact us all.

NARROWING THE KNOWLEDGE GAP

The Fogarty International Center is the leading edge for the NIH internationally. The Center is widely respected for its work to promote science for global health. As in the poster (figure 1) that is up at the moment, in the April 2002 issue of The Scientist, a profile of the Fogarty International Center subtitled "The Seeding of Third World Science" will demonstrate, science is inherently international and discovery knows no borders.

[The information follows:]

The Scientist

The Scientist 16[7]:50, Apr. 1, 2002

PROFESSION

The Seeding of Third World Science

The Fogarty International Center trains developing-world scientists to research health care problems

By Bob Calandra



Sowing Seeds Profes sor Jo nathan R. Stream s III (right) of the University of Pennsylvania oversees research at Chile n related sites Juan Emilio Schwarze.

Last August a contingent of US AIDS researchers visited Malawi, where health officials believe 20% of the adult population is HIV infected. The investigators wanted to know if government leaders would allow officers to pick people for AIDS vaccine trials set to begin later this year. After meeting with the nation's top three health ministers, the visiting scientists were surprised to find that each were former Fogarty International Center (FIC) fellows trained at Johns Hopkins University. "The other investigators turned to me a nd said, 'I don't even have to finish the AIDS effect that you've been to talk about'" says Chris Beyrer, an associate professor Johns Hopkins Bloomberg School of Public Health and member of the Malawi team. "I had a good one so that we had had a big impact there. But it kind of surprised me."

The presence of Fogarty scholars shouldn't have surprised Beyrer. Johns Hopkins has been a part of the Center's many programs across AIDS is developing countries since it's inception. In the years since, Fogarty has underwritten the training of most, if not all, of the leading scientists in AIDS research in US-sponsored AIDS centers in developing countries. We are devoting the major part of our resources to research and research training in developing countries where the burden of disease is greatest and the resources are the most limited," says Fogarty director

"We are devoting the major part of our resources to research and research training in developing countries where the burden of disease is greatest and the resources are the most limited."

The Fogarty International Center is one of nine institutes and centers that develop Third World disorders. 1,200 members of seven Molecular Biology Dep artment (EMBO) undertake short courses, workshops, and lectures, but also offers long-term fellowships and operates a young investigator program, which aids recipients dependent rates into a broader science of training. "We are giving our fellowships to researchers in developing countries to some more a research

The British Medical Research Council has had at least seven of labs in the Third World. The NIH works with the Department for International Development (DFID) to sponsor a $16 million, five-year international research collaboration among researchers in South Africa, Tanzania, Uganda, Caribbean, Zambia, and the United Kingdom to develop new children, vaccines that could prevent approx imately 199 and other sexually transmitted diseases. The 5-weeklong government who finance of 100 million (€106 million) expenditure clearly, play world health research in 2000.

While few question the merits of such programs, some argument say agencies should target their federal funding be aware of silent crises. Many Third World

The vast majority of Fogarty's trainees return to their homes, where many become nationally renowned leaders in science and medicine.

Conception to Contraception

Originally conceived by former US congressman John E. Fogarty (who believed that "just as disease knows no boundaries, so also the benefits of medical research and trained research is of the know-no benefit nor," the center opened in 1968. Initially the focus was between developed countries or in Latin America where education was particularly advanced. Much has changed in the past 20 years that perspective has changed. The heavily distressed parts of the world which FIC researchers don't go as much important. But perspective has changed to focus global science to aid the critical issues in global health."

That change in mission led to Fogarty's completion of the Office of HIV/AIDS in 1988 the Center became which is now its largest training program. The AIDS program is only one of the many research projects on which the agency spends $40 million ($70 of its $146 million fiscal 2002 budget. The remaining money will be used for staffing, conferences, and researching viruses around the world.

The necessary and networking services help scientists locate developing countries as they do each of the latest developments while connecting relationships in for-to-ed to countries. Lots of cooperation and collaboration around the globe, according to Fogarty fellows said staff. "We can be a handy and you don't have contact with your body" says Juan Enrique Schwarze, a Chilean working for a lab at the Center for Reproduction and Women's Health at the University of Pennsylvania. "These are contacts that you never lose."



Fogarty Fellows Pedro Fernand (left) and Jo nathan F. Stream s III (right) in his University of Pennsylvania laboratory.

Schwarze is one of 12 Fogarty investigators in Peru working under Jonathan F. Stream s III to harass young scientists in certain cognitive, reproductive hospitals and sentinel child a lab. The FIC follows Let Peru some of them from Latin America are picked while the year "We bring the people and take care of her two to two years periods of training and likely work over the guidance of a faculty member," Schwarze says. "We have had some fairly senior people have an respect to their training. They are now guiding financially from their organizations now."

Garnering Human Capital

When they don't make monetarily the fellows make up for in new skill acquisition, according to Stream. Seen as risk pools in the $36,000 per year Global Health Research Program, a competitive exercise that helps young foreign scientists learn how to apply and get training, structure of research and other funds, Fogarty started the program as an enjoying 600 developing-world fellow scientists on the NIH campus with a budget of $ 16.5 million for training for scientific ways. "We have had a tremendously favorable response to this initiative," Stream says.

Stream says his staff does everything possible to help the scientists move they return to their home countries, from evaluating science to papers ongoing over

But the scientists, not the money, are the real seeds planted by FIC in the world's poorer nations. The first crop has already started to bloom.

Seeding Science's Future

But the scientists, not the money, are the real seeds planted by FIC in the world's poorer nations. The first crop has already started to bloom. Harris Pratt, an immunologist at the Thailand army, Johns Hopkins and Fogarty he was had with scientists for 14 years. "We've ons in the second generation including whom the FIC helped in Laos and with funding in Chiangi Fogarty," he says. "Instead of continuing to collaborate they are getting trained in Thailand.

Fogarty's [illegible] develop technology to collect and analyze [illegible] research. The FIC also seems sound as [illegible] many wants to see the best strengths as [illegible] as well as supported in."

Bob Calandra is

1 T Clarke, "NIH is advised to expand its international ac tivities," The Scientist 14[19], March 3, 1997.

Figure 1

NIH collaborated research conducted abroad is essential for Americans. Research on tropical infectious diseases that may affect travelers, businessmen or our military cannot be done in the U.S., and research to better prevent mother-to-infant transmission of HIV is most definitively done where, unfortunately, the burden of disease is greater than it is here.

The Fogarty International Center also ensures that this research is of the highest ethical standing and of mutual benefit through its training programs and research ethics.

Sometimes overlooked is the important role of science as diplomacy. Fogarty currently supports research by a U.S.-Israeli-Palestinian team to identify genes for hereditary deafness in the susceptible bedouin population. As featured in the New York Times last week, this project is an example of bridging the enormous gap of politics through scientist-to-scientist relationships developed by working together on a shared agenda.

Science training also trains leaders. As one of many examples, Dr. Crisps Kiyonga, Chairman of the Global Fund for AIDS, TB and Malaria, was an earlier trainee in the Fogarty International AIDS training program. His experience in Uganda, using the knowledge gained through collaborative research to identify interventions that would really work, is essential to the future of this global initiative.

SCIENTIFIC COLLABORATION ON GLOBAL HEALTH

Today's theme is collaborations, and these are at the very center of the Fogarty. The next poster (figure 2) are diagrams—just three—of our Fogarty global programs on AIDS, tobacco use, prevention and cessation, and environment and health to illustrate how essential collaborations are. They involve other ICs across the NIH, other parts of the Department of Health and Human Services and a multiplicity of outside organizations. Each of the spokes you see represents a collaboration between Fogarty and a partner.

[The information follows:]

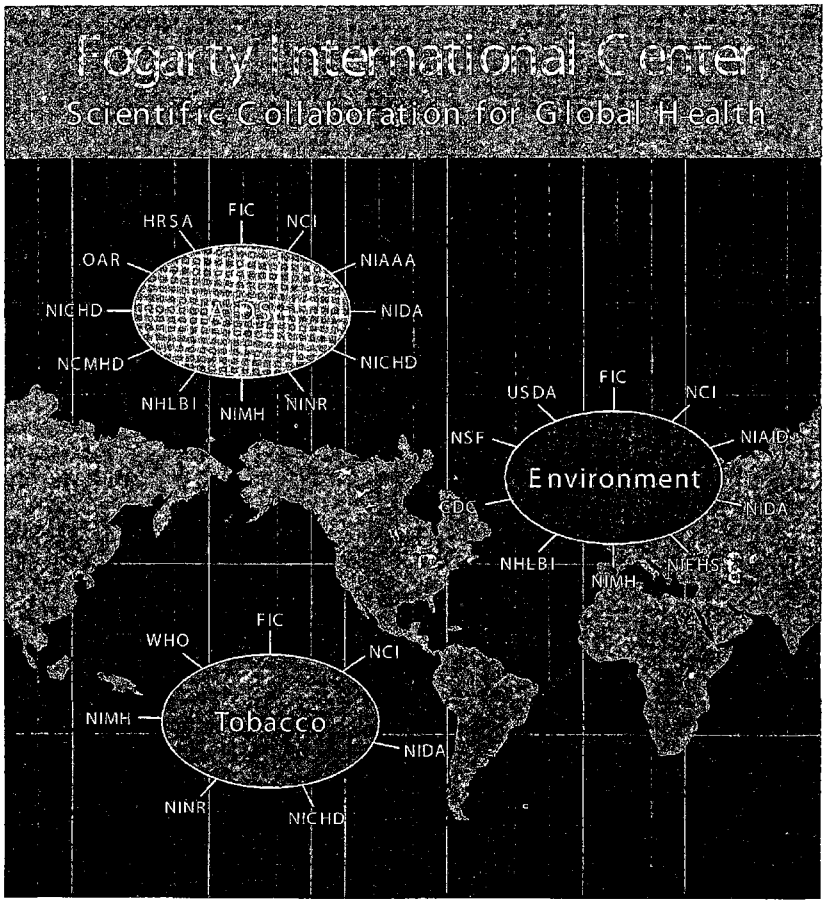

Fogarty International Center
Scientific Collaboration for Global Health
HRSA
FIC
NCI
OAR
NIAAA
NICHD
NIDA
NCMHD
NICHD
NHLBI
NIMH
NINR
AIDS
USDA
FIC
NCI
NSF
NIAID
Environment
CDC
NIDA
NHLBI
NIEHS
NIMH
WHO
FIC
NCI
NIMH
Tobacco
NIDA
NINR
NICHD

Figure 2

These three programs alone involve 65 countries around the world, primarily low- and middle-income nations and including Eastern Europe and the former Soviet Union. The programs are based on close collaborations and networking between U.S. and foreign teams of scientists. It is entirely apt to say that for Fogarty and for the other ICs at the NIH engaged in international research that collaboration is a way of life.

I will be happy to answer any questions you have about these or any of the other Fogarty programs, as well as our plans for the coming year.

Dr. KIRSCHSTEIN. Mr. Chairman, we are prepared to proceed as you wish.

Mr. REGULA. Dr. Kirschstein, would you characterize these as clearinghouses to assemble activities that are happening in many different areas?

Dr. KIRSCHSTEIN. These are our ability to use clearinghouses. We use the word "clearinghouse" in a very particular way among the institutes. It is something in which information is deposited and can be sent out to the public as needed. And most of our clearinghouses are on Web sites or are used by people who answer telephones and so forth, and some of them are ordained by Congress. But in general all of the information is sent out in the form of some sort of clearinghouse, yes.

Mr. REGULA. Well, if you had a question on let us say osteoarthritis, would you go to Dr. Katz's agency?

Dr. KIRSCHSTEIN. Each one of these institutes is characterized as being the lead institute in these collaborations. Dr. Katz started off by saying the major collaboration is between the Arthritis Institute and the Aging Institute. It is the disease plus the population that is most affected. But there are many other collaborators, and Dr. Katz will serve as the clearinghouse to be able to field the information.

Mr. REGULA. So it is, in a sense, one-stop shopping for the public that wants information on a particular subject? They can go to any one of these agencies and elicit that, and they can learn from that what is happening in the private sector as well as the public sector?

Dr. KIRSCHSTEIN. That is correct, provided what is going on in the private sector is known to us.

But in addition we have at NIH some central clearinghouses which will provide information if the caller, for example, does not know exactly what institute he or she wishes to have things referred to. We have all our clinical trials listed on a clinical trials.gov database on the Web, to which anybody can go on the Web, if they have access—and I understand, they don't all have it—to get information.

Mr. REGULA. Would that include information from outside the United States?

Dr. KIRSCHSTEIN. Yes. The requirement for the clinical trials database and information service was set up under the Food and Drug Administration Reauthorization Act several years ago, but the responsibility was not given to the Food and Drug Administration. It was given to the NIH, which, in turn, gave it to the National Library of Medicine, because it had the widest ability to set

something up in that regard; and Dr. Lindberg, who is the Director of that institute, will be here for our final hearing, which is communications, and will be pleased to address that.

PUBLIC INQUIRIES TO NCCAM

Mr. REGULA. I know for a period of time, at least in my area, people thought there was a magic cure for cancer in Mexico; and they would actually go to Mexico, and it didn't necessarily pan out. But would they be able to access your agency and find out what was being proposed in Mexico?

Dr. STRAUS. They not only would, but they do so on a daily basis. It is a toll-free clearinghouse by telephone and Web and provides information to about 7,000 Americans just through the clearinghouse, and 1.25 million inquiries to our Web site each year.

Mr. REGULA. You get the same thing on various drugs and magic potions, if you will, for health cures.

Could someone who reads or hears about that check it out through your Web site?

Dr. KIRSCHSTEIN. That's correct.

Mr. REGULA. And they could access a Web site that would be sort of a master source of information and, in turn, could go to osteoarthritis or to cancer.

Dr. KIRSCHSTEIN. And we have an index of these, which is on the Web site for the Office of the Director, Office of Communications, specifically.

OSTEOARTHRITIS TREATMENT

Mr. REGULA. Let me ask you about osteoarthritis. Somebody was telling me that for knees, they have an injection system, some kind of a material that ends up replacing, if you will, the cartilage; is that true?

Dr. KATZ. I think what you are talking about is Hyaluron, a product that is being produced by a few different companies and in the short-term studies that have been reported, there is some benefit with regard to pain. With regard to its modifying the disease, that is not very clear. But with regard to short-term pain improvement, two studies have shown a significant improvement.

Now a significant improvement is not a tremendous improvement. These two medications that are injected into the knee are made by two different companies. Some of these products were developed in Europe and then were adapted by the United States.

Mr. REGULA. So you do collate information from around the world?

Dr. KATZ. We do. We all do. I think it is important to know that there are so many proposed treatments particularly for osteoarthritis and other chronic diseases, that there is no way we can provide information on all of the inquiries that we get. There are many, many drugs, devices, and interventions that we are asked about in terms of whether they are efficacious or not efficacious.

We report on what we, with the community, come to realize is an effective therapy. We have informational booklets; all of those booklets are available on the Web. Interestingly, we are getting more inquiries percentage-wise from the Web than paper inquiries.

We have booklets available in other languages as well, so that more of our population has access to the information.

PUBLIC INPUT

Mr. REGULA. Do you get feedback from the public as to what works?

Dr. KATZ. We get many suggestions from the public as to what we should try in terms of doing studies, and I am sure Dr. Straus probably is the champion of all of these suggestions.

Dr. STRAUS. Obviously, our center is studying modalities that are popular, and that the public is interested in, but which are largely untested and certainly unproven. But we do go out and solicit feedback from the community as I indicated several moments ago. We have held three national town meetings. The last was held last month in Portland, Oregon; 700 members of the public came to tell us what they are interested in hearing about, what they want to see studied, as well as some of their own anecdotes.

There are often germs of wisdom in some of those popular choices.

PUBLIC INQUIRIES

Mr. REGULA. I notice the proliferation of stores that sell magic potions for health, all types of things. If a member of the public contacted you via the Web site and said, does XYZ really do what the allegations say it does, what would your answer be? How would you respond?

Dr. STRAUS. We do respond to that question every day, Mr. Chairman. It turns out we already have about four dozen summaries of statements and reviews of data on the most popular questions that are asked, dealing with arthritis and pain and cancer and the like. There are, unfortunately, areas that are not studied and sometimes our answer is simply that the person has to be somewhat skeptical about something whose claims sound too good to be true, because they often are.

ACUPUNCTURE

Mr. REGULA. Does acupuncture have merit?

Dr. STRAUS. Acupuncture is a venerable practice and people have used it in Asia for thousands of years. But today the best evidence about acupuncture is that it is probably a good alternative form of relief for certain kinds of pain disorders—not for everything for which it has been touted. It does appear to benefit pain—and we are getting more definitive answers with degenerative arthritis pain in the large study I mentioned that we are conducting at the University of Maryland at Baltimore.

And we are beginning to understand the mechanisms by which acupuncture works using very sophisticated brain imaging technology.

It is clearly an active modality. It certainly appears to benefit some people. The question is whether it is superior to other standard treatments.

Mr. REGULA. Mr. Obey.

Mr. OBEY. Mr. Chairman, Dr. Straus indicated that sometimes scientific claims are without merit. I think it is safe to say that that is often the case in politics as well. I think you mentioned Mr. Chairman, the fact that some people used to go to Mexico for a magic bullet for cancer. I can remember when laetrile sales were used to finance real bullets for Posse Comatatis and militias back in my neighborhood—some pretty nasty stuff.

Dr. Kirschstein, in your statement, you said the existence of the National Institute of Biomedical Imaging and Bioengineering is rooted in collaborations and then you listed the various Institutes. I agree with that. But I frankly have to confess some concerns about the creation of that Institute and the creation of a number of other Institutes, because we have had a tremendous proliferation of Institutes through the years. I am not convinced that all of that is for the good, because it leads to more administrative costs and it can lead to fragmentation.

When I look at the House Democratic Caucus, I see Democrats identified as "New Democrats," as "Blue Dog Democrats," as "Progressive Democrats," and I don't think that any of those monikers especially add to our effectiveness. I think they do emphasize our fragmentation.

GRANT TRANSFERS TO NIBIB

With that skeptical mind-set in mind, let me ask you a couple of questions. I understand that NIH is in the process of reviewing existing research projects to determine which will go to the new Institute and which will stay with existing Institutes. It seems to me that those decisions call for careful balancing, because on the one hand you have the fact that the Institute was created in order to provide a central home for basic, crosscutting research and imaging, and yet on the other hand those technologies are important not for their own sake but what they can help us to understand about other diseases. And I think it would be unfortunate if the establishment of a new Institute led to the artificial separation between scientists with expertise in particular diseases and scientists with expertise in the technology that is supposed to help us diagnose and treat those diseases.

Could you tell us a bit about the criteria that would be used to determine which projects go to the new Biomedical Imaging Institute and which stay in the disease-focused Institutes? How are you approaching the problem of using new Institutes to help stimulate technological advances without creating an undue separation between work on technology and work on the substantive problems that the technology is supposed to help solve?

Dr. KIRSCHSTEIN. Mr. Obey, we share your concerns and we have shared them from the beginning. The purpose of several of the Institutes that have been in existence for quite some time is to support multidisciplinary, interdisciplinary research, particularly in technologies. There is and has been a proliferation of Institutes over the years and there has been some concern. The Congress has expressed that concern, and as you know, the National Academy of Sciences will be undertaking a study of this at the behest of Congress to start. Now that a Director has been nominated, just about

immediately because it is expected to report within one year of the Director taking office.

However, after careful deliberations, the Congress in its wisdom decided that this new Institute should exist and—

Mr. OBEY. I am not so sure how careful those deliberations were.

Dr. KIRSCHSTEIN. Yes, sir. I understand.

It is our mandate to try to do that without disruption of many things. This was true way back when the Eye Institute was formed out of the Neurological Diseases and Blindness Institute, when the Deafness Institute was started out of the Neurological Diseases and Stroke Institute, the word "blindness" having been removed because the Eye Institute had been formed and so forth and so on.

I believe we have to work very hard to make sure this new Institute succeeds and does not diminish, but enhances the activities of all the other Institutes; and Dr. Dean and I have been doing that. We have just completed the search for a director of the new Institute, and I have made a recommendation to the Secretary that I think everybody will applaud.

That said, the decision about what is to originally be transferred to NIBIB was put in report language that this committee gave us as to how we should go about that procedure. Indeed we had a meeting that was requested by our oversight committee and their staffs to talk about this. The criteria was set based on a series of well-developed strategies, which have always been used when new institutes are established. First and foremost, to develop a mission statement.

DEVELOPMENT OF NIBIB MISSION STATEMENT

And we had a number of Institute directors, at least one of whom is sitting at this table, Dr. Katz, along with Dr. Dean, who we had determined would be the acting director in the period before we searched for the new director, put together a mission statement. The law required that there be a transfer of grants upon the establishment of the new Institute. And it was directly stated in the law and not just in the conference language or report language.

Dr. Dean then developed a list of search terms from our mission statement that everybody had agreed to. She fed them into our computer base that puts grants forward; and we had an agreement between ourselves and members of the Congress as to how we would constitute the group that was going to review those grants. The working group developed the criteria from the mission statement. We are still in the process of doing that review and have not completed it, but we are working very carefully and very hard.

MULTIDISCIPLINARY AND INTERDISCIPLINARY RESEARCH

We are as cognizant as you are that there is a great deal of importance in doing research on imaging, and on biomedical engineering in particular diseases, research which is closely associated with those diseases. There are a series of about six Institutes which have a major interest in those areas. In fact, as we have gone through the process, it clearly shows that some of the material that is being supported in the six Institutes is there because there was no home for the developing technologies. Not even a home in one

of the two Institutes which usually has been given that responsibility.

If Dr. Dean wishes to expand on that, I would be pleased to have her do so.

Dr. DEAN. I would like to offer one particular comment that I have.

Among my Institute colleagues over the last year, I have been very careful—and I believe very strongly that the NIBIB, as we are building it, will be adequate to, will complement what is already happening at the NIH and will not detract or subtract from the other missions of the other Institutes.

What I have found particularly gratifying, as I have been to probably more than 40 professional meetings of engineering, physics, optical societies over the last year, is to tell them about the new Institute, about the number of physicists, engineers, mathematicians, other scientists, who have never come to the NIH before for research grants and who are now looking to the NIH as an area of opportunity. I think that is one of the missions that we can build our new programs on.

I am also pleased to say that we have developed two new programs for Requests for Applications (RFA), and the response to that has been overwhelming. I think we are—as any new organization would be, showing our way. We are developing new areas, and the path is not always as smooth as I think all of us would like it to be.

Mr. OBEY. Let me simply say that it is not that I was opposed to the creation of the institute, but I recognize that the Congress is the possible instrument by which political pressure is brought to bear on scientific questions; and often that pressure is in the wrong direction and it meets more the political needs of the participants than the medical or scientific needs of the public.

And so I guess all I would say is, I assume you recognize that the conference report language is considerably softer than the original Senate version.

Dr. KIRSCHSTEIN. Very much aware of that.

Mr. OBEY. And that the term "should generally reside" leaves an awful lot of room for interpretation. And I guess my advice would be, go slow and use caution.

Just one other question on this. There have been reports in the press and elsewhere that some Members of the Senate and the House are actively campaigning to have all or part of this new Imaging Institute located not on the NIH campus but in another location. Am I correct that no such shift is currently being proposed by NIH or the administration?

Dr. KIRSCHSTEIN. Correct.

Mr. OBEY. I am pleased to hear that. I think that the White House and the agency made the right decision to date.

Secondly, without wanting to put any of you on the spot about this or any other specific proposal, could you comment generally about the merits of keeping the NIH intramural research program largely together in one piece and the disadvantage of dispersing various activities to various parts of the country. As an example, let me tell you a story.

My predecessor on this committee, Mel Laird, was very interested in seeing that the new Institute of Environmental Health Sciences be located at the University of Wisconsin, and so he arranged to make certain that there was a geographical description of where it could not be, paving the way for the University of Wisconsin to run the show. It didn't quite turn out that way.

Dr. KIRSCHSTEIN. I was there at the birth.

Mr. OBEY. Being from Wisconsin, it would have been personally delightful to me to see it located there. I think from a scientific standpoint it is never good for the Congress to determine where this research ought to take place because those decisions would be political rather than scientific.

Dr. KIRSCHSTEIN. And I think the institute you are referring to, part of the reason when it ended up being in North Carolina rather than in Wisconsin—it did succeed, and I think it would have succeeded in Wisconsin, as well—is because it was an institute that grew out of the National Cancer Institute, which had had responsibilities for many, many years and therefore the major staff and people had had experience being with NIH as a whole and were able, although not as easily as they could have if they had stayed on the campus, to operate because they knew what was going on.

I felt particularly strongly about an institute that really had no roots for a long period of time; and at any one unit in NIH—and how difficult it would be for that institute and that intramural program, in particular. Because all the intramural programs, although they are all associated with the individual institutes, work together, have a dual reporting authority not only to their institute directors, but to the Deputy Director for Intramural Research at NIH, it would be very, very difficult to have that happen at the new institute and it would be to the detriment of the institute, of its intramural program of the State that wished to have it, and of NIH in general and the American citizens.

So we had a great deal of discussion and came to a solution that I think will work quite well, which will be to help the various organizations around the country, both those who want to have intramural activities that will remain at NIH—and, in fact, we originally didn't set up an intramural program for this institute at all—not every institute has one—because we thought the major concern was to provide a home for the people that Dr. Dean has been talking about, namely the physicists, engineers, optical scientists, radiologists, academic institutions across the country.

Mr. OBEY. Mr. Chairman, I will put some other questions in the record. Let me simply say that we can have lots of differences on this committee, philosophical differences and political differences, but I think the most important accomplishment of this subcommittee since it has existed has been that it has on almost all occasions—not all, but on almost all occasions, it has resisted efforts on the part of Members of Congress to put their mitts on health research.

It is one thing to be supportive of health research. It is another thing to have politicians directing what research ought to be conducted and where it ought to be conducted. If we get into that business, we will rapidly discredit ourselves.

Mr. REGULA. Mr. Sherwood.

Mr. SHERWOOD. Thank you, Mr. Chairman.

BACK-TO-SLEEP CAMPAIGN

Dr. Alexander—and it gives me great pleasure to say that because the country doctor that ministered to us all in the small town I grew up in and was a great effect on our community was a Dr. William Alexander. You have done such a great job with your publicity campaign on the Pampers and Gerbers for your "Back-to-Sleep" campaign. You are to be commended. I think that is great public relations.

That is getting the message out, and that is one of the things we have talked about on this committee several times, that it is very difficult to get the message of the new and best treatments to where it ought to be delivered.

OBESITY IN CHILDREN

And in that regard we have heard so much about obesity in children, and it is leading to early diagnosed Type 2 diabetes, and it is really an epidemic. What Federal, State and private agencies are you working with to help parents and schools and kids do a better job of getting and staying fit? In other words, what would be the magical deal like you did on "Back-to-Sleep" that we can do on obesity in kids?

Dr. ALEXANDER. Mr. Sherwood, I wish there was something as easy that we could do for obesity. It was just a matter of which position we put an infant down to sleep in; that was one of the easiest behavioral modifications. The subject couldn't even object very easily to it, and so it was relatively easy to implement.

And we really have to thank the partnership that we got with industry. They put that message on the cereal boxes, free; on the diapers, free. That was their public contribution to public health, and we owe them a big thank-you for helping to get that message out so effectively to change the sleep position and, consequently, change the SIDS rate so dramatically.

Dr. ALEXANDER. Obesity is harder. It is like stopping smoking. It is like some of the other health behaviors that are very difficult to change. What we are seeing as a new phenomenon is the enormous increase in obesity among young people, and this is due to a combination of factors. Partly it is increased caloric intake, but much more significant has been the reduction in physical activity, physical exercise. If you look at overall population data, caloric intake has not increased that much. It is much more a reduction in caloric expenditure resulting from less exercise.

Secretary Thompson has been extremely interested in this topic. He is greatly concerned about the increase in diabetes, Type 2 diabetes in children in particular, and the increase in prevalence of obesity. He wants to put the whole department on a diet; so we are all walking around very carefully, tummies tucked in and things like that around the Secretary. He is interested in focussing this on children, on schools, and has a task force convened to look at things that can be done. One of the things that is being looked at is physical education, and physical activity in schools.

We are in the midst of a phenomenon where physical education has virtually disappeared from the Nation's public schools. Where-

as it used to be a routine part of every child's day, elementary school through high school, it is now less than 20 percent of middle and high school students that participate in physical education. So there is a move afoot to try and restore physical education as a requirement in elementary school through high school.

There is a movement also related to the school lunch programs in terms of their caloric content, their fat content and some other activities. There are also activities planned in conjunction with the Department of Education and the Department of Health and Human Services in trying to improve the education of children and of their parents in terms of what they send to school in their kid's lunch, and an increase in education with regard to the importance of physical exercise, physical activity and that side of the coin, not just the caloric intake part.

Mr. SHERWOOD. I think you are on the right track when you try to do it through the public schools, and with many years of public school board experience, I think some of the things that we have done that we thought were progress have been counterproductive. We now bus kids to school when they only live a half mile away and you never used to do that, and where there are safety issues. But what they eat and the soft drink machines in the schools and things like that are counterproductive, and I think we gave physical education a bad rap maybe as we tried to improve our academic standards. A very necessary move to try to improve academic standards, we shortchanged that.

So I agree with you that the public schools is the place to go about this. And I think anecdotally, I think caloric intake is certainly different than it used to be. I think when the chairman and I grew up, we didn't have a lot of those things available, and so anything we can do in that would be great. I have one other thing that I would like to talk with Dr. Dean about. I know one of the greatest challenges that are faced by health care providers at home in northeastern Pennsylvania is finding trained medical technicians who have mastered biomedical imaging equipment. And in developing relevant standards and guidelines for this equipment is consideration given to ease of use and level of training required of operators.

Dr. DEAN. Yes, Mr. Sherwood. And in fact, one of the areas of the law that established NIBIB said that we were to pay attention to those critical issues as we develop our programs. One of the most tangible things that we have done is that we have entered into support of a study with the National Academy of Engineering, which is going to be looking at the facilitation of what we know in imaging and engineering research into improving the Nation's health care delivery system.

We were very pleased to partner with them in that activity, and we are hoping, through that partnership with them, to identify those things as you referred to as standard-setting, how those can be widely deployed across the Nation and used.

Another area of interest that we have within NIBIB is to explore the advances in telemedicine and teleradiology and how that technology can be used to employ the delivery of high quality medical care to rural citizens and other underserved populations. So while I cannot tell you explicitly that we have a whole portfolio of pro-

grams that NIBIB can roll out today, I will tell you it certainly is an interest of NIBIB. It is a personal interest of mine, because I grew up in a rural underserved area in eastern Kentucky, and I truly appreciate the problem, but also recognize there are wonderful opportunities to create solutions.

Mr. SHERWOOD. Thank you. I don't think I ever understood what the term "user-friendly" meant until I tried to get into the 20th century on my personal ability to operate computers, and then you realize that our military services for years have tried to standardize things and make the directions crystal clear and make it simple, and I think anything we can do in our biomedical imaging stuff in that regard would be good.

HEALTH DISPARITIES IN RURAL AMERICA

Dr. Ruffin, in the line that we just started on, I understand that your center studies health disparities, and are you aware of any good studies into health care access in rural America? I am well aware of the anecdotal reports of such disparities, but have there been any findings that you are using and could recommend policy changes to make health care more available in rural areas?

Dr. RUFFIN. Mr. Sherwood, the creation of the new center broadened our mandate to address health disparities not only in racial and ethnic minorities, but also in other populations, such as those in rural America.

And we are now beginning to attack that issue the same as we did as it relates to the minority population, and that is that we are beginning now to go out into those communities to identify what it is that we ought to be doing in those communities that we are not doing and then coming back with that information and partnering with the NIH IC's to develop new initiatives to deal with those issues. There are also several congressionally mandated programs, we are putting in place. For example, the loan repayment program establishing Centers of Excellence in communities around the country to deal with these various programs. We are now bringing technical assistance workshops to the communities around the country to make them aware of these programs.

Health disparities we find in one part of the country are vastly different than those found in other parts of the country. So we are trying to pay some attention by listening to the individuals in those communities and asking a very simple question, what is it that we ought to be doing in these particular communities that we are not doing. We are beginning to get some feedback on that and working with our partners to collaborate to develop models and programs that will address these needs.

Mr. SHERWOOD. If you have any good information there that you would like to forward to my office, I would be glad to look at it.

Dr. RUFFIN. Thank you, sir.

Mr. SHERWOOD. Thank you, Mr. Chairman.

Mr. REGULA. Mrs. Northup.

Mrs. NORTHUP. Thank you, Mr. Chairman. Let me start with Dr. Dean, and thank you for your visit to Louisville. I understand you were coming back to the State where you apparently grew up but coming to our city meant a lot. I am interested in the issues of mental health and bioengineering and I know the chairman and I

had a conversation recently about this, but in deference to some of my fellow committee members who have talked about mental health parity for a long time, and their concerns obviously are evident to us all.

I have the anecdotal experience of all of us that meet with people in our district that have concerns for their children, their families, other members, and inevitably it seems like the discussion of people with mental illness being able to stay on their medications are hugely important, and yet I am not aware of any sort of timed-release bioengineered thing that we are developing for, say, diabetes, for other things, slow release efforts, and I just wondered if there are efforts that I am unaware of.

The professionals in my district talk about the difficulty of even researching mental health because of the difficulty of making sure that you know exactly what your research population is taking in order to see whether it is working, whether it needs to be changed, and it just strikes me that when I talk to families who, in particular, have just really terrible concerns that often they find they can get their child stabilized, they can get their family members stabilized, they then get out on their own, get off the medication, and get into a crisis again.

Dr. DEAN. I can provide a response but I suspect it will not be an answer with the clarity that I would like to be able to give you. First of all, I would say that NIBIB has entered into a number of research partnerships with both the National Institute of Mental Health and the National Institute of Neurological Disorders and Stroke in generating new research grant applications that probe the application of engineering and imaging approaches to assessing central nervous system function and mental health. But I would speak from the engineering imaging side is that I think there are significant opportunities in the imaging arena, particularly the functional neuroimaging arena to identify brain function, and perhaps aberrations that would be outside the norm of brain function. I think there are a lot of opportunities there. I am very excited by what the Mental Health Institute folks tell me they see as opportunities for developing new drugs from their perspective.

I won't comment on the drugs that are needed because I am not expert in that area. I will say secondarily that one area that NIBIB sees that we can develop and foster in a trans-NIH way is the general area of biomaterials because we see the opportunity to develop new materials that perhaps could be used in controlled drug delivery release of various kinds of drugs.

Earlier, one of the projects I highlighted is actually microneedles that actually could be used to deliver insulin for diabetes, but this same technology, once it is matured and can be used in humans, could also be used to deliver things such as vaccines or small particles that could do controlled release of medications.

Mrs. NORTHUP. I guess my concern is I don't see this being applied. I understand the imaging is a different question, and maybe yours isn't the right institute to be asking this question of, but I do not see any effort being made to develop the delivery of these drugs for mental health issues, and I would say it is the one area where, while I don't share some of the parity issues that other members of this committee do, it strikes me that it might be that

nobody is trying to because there is not any money in that area and so let me just say again can you answer for me whether any of these sort of slow released or other applications of drugs are being tried with the treatment of mental health?

Dr. KIRSCHSTEIN. Ms. Northup, we will ask Dr. Nakamura of the National Institute of Mental Health to provide you with the answer. I think it is going to be yes, but I would like to make sure and have him answer.

[The information follows:]

SLOW RELEASE DRUGS AND MENTAL HEALTH

Dr. Nakamura: Adherence to treatment is a critical aspect of mental health care, as it is in other medical care. Unfortunately, lack of adherence to treatment is common in mental health care and is a significant contributor both to inadequate improvement and to recurrence of episodes of mental disorders such as depression, mania, and psychosis. Research indicates, for example, that fewer than 50 percent of patients who are prescribed an antidepressant continue taking it for longer than 6 weeks, despite evidence that antidepressant treatment should last for at least 6 months after full remission of symptoms. Long-acting, slow-release formulations of drugs could address this problem. Over the years, a number of slow release formulations for antipsychotic and antidepressant medications have been developed by the pharmaceutical industry. Antipsychotic medications are available for which a single dose is therapeutically effective for as long as four weeks; for antidepressants, formulations with 24-hour effectiveness are a vast improvement over the need to take medications two-to-three times daily. Extended release preparations of stimulant medications for attention deficit hyperactivity disorder also have been approved and now are being marketed.

The actual effectiveness of slow release medications is currently being investigated in several large clinical trials treatment studies funded by the National Institute of Mental Health. Slow release preparations of antipsychotic medications are used in the Clinical Antipsychotic Trials of Intervention Effectiveness project (CATIE) in schizophrenia, which is run at multiple sites across the country and aims at recruiting up to 1,600 patients in the next 4 years. Likewise, slow release antidepressants are used in Sequenced Treatment Alternatives to Relieve Depression (STAR*D), a multisite trial for patients with major depression.

Mrs. NORTHUP. I would appreciate that, because it is possible that I may want to talk about some language in the bill this year that——

Dr. KIRSCHSTEIN. There certainly are slow release things for other diseases, the pump for diabetes and so forth, but we will get specific answers related to the mental health situation.

BOTANICAL-DRUG INTERACTIONS

Mrs. NORTHUP. Thank you. I assume I have a few more minutes, Mr. Chairman. There are two other areas I will try to hit very quickly. One of them is alternative medicine, and I can't thank you enough for the advancement of the new therapies and alternative medicine. I remember the first year I was here, I asked about it and I think it had not been started, and clearly it is a much more aggressive institute for you all now.

I will tell you a story of traveling with about eight friends, and we all arrived at breakfast in the morning and literally poured out into our hands all the vitamins that we take, and when I started running a year ago, my hip started bothering me about 6 months ago, so the first thing I did was get on the Internet and I found chondroitin and glucosamine and have been taking that. It is a miracle. I have never stopped running one day, and it is all gone, but if that hadn't worked, I was going to go to acupuncture. And

I would have gone to a doctor sooner or later. I am sure the doctor would have said don't run for 6 weeks, which is what kept me from starting there, but I just think that very many Americans you can just look at the catalogues on the development of these drugs.

My question is what are these things doing to my liver and my kidney? And if we don't research these, we are going to be running fine. It is the other parts of the body that——

Dr. STRAUS. If I may, Mrs. Northup, let me say your point is well taken. Americans are captivated by easy solutions, something in a pill that would take care of their diabetes, their overweight——

Mrs. NORTHUP. Eternally young.

Dr. STRAUS. Eternally young. We have come to expect to remain fit forever because biomedical research has given us so much in the past century and we want the rest.

The problem we have is these products that are in the public domain have not been tested. We at the NIH are interested with our partners not just in whether they work but how they work and exactly, as you said, what else they are doing. For example, you may know that the FDA posted an alert about Kava a very popular herbal product for anxiety, several weeks ago because reports throughout the United States and Europe suggested that it may be associated with rare but very serious liver injury.

We are funding studies of Kava, looking at basic mechanisms and what it does to liver cells. We have put our clinical studies on hold for a moment pending an analysis of some of the safety data to be sure it would be ethical to proceed. We have completed today, and you will see in the press tomorrow, results of a major study of St. John's Wort for the treatment of depression. Before finishing that study, our colleagues at NIH and grantees around the United States studied St. John's Wort as a natural substance. It might be effective but it does interfere very potently with the body's metabolism of important drugs, AIDS drugs, birth control pills, cancer drugs in a report from——

Mrs. NORTHUP. So if you weren't depressed before, you might be depressed after——

Dr. STRAUS. That is right. If your birth control pill fails, you now have a reason to take St. John's Wort.

Mrs. NORTHUP. I really appreciate that. I am somebody who believes you should be able to buy the vitamins and so forth, but I think that all of us want to be warned and I guess the week before elections I shouldn't take Kava, no matter how stressed I feel?

Dr. STRAUS. Probably not. But the issue of the message to the public, I think the American public wants not only a quick answer, they also want the correct answers. The packages of these products say "the product has not been shown to be safe or effective by the Food and Drug Administration. That is not exactly the information the public would like to be armed with. We hope to arm the public with statements like "please avoid using it in the following context: With this medication, with this health condition and expect it to be effective only under these circumstances * * *" just as we do for all conventional medicines.

READING READINESS

Mrs. NORTHUP. Thank you. And finally, if I could just comment on the National Institute of Child Health and Human Development, Mr. Chairman, we are spending probably the biggest increase in dollars in defense, secondly in education. And the question is primarily, how do we make sure every child succeeds in school and it starts with how do we make sure they are ready for school; and secondly, when they get there, how do they succeed? And the more you spend money, the more I find you have a line outside your door with people that have the program that they believe will make sure that every child succeeds in school.

And the best thing we could do for us to make sure that our dollars are spent in the best way, not only so we get a return on our investment, but so that every child who is 6 years old really does get the best education possible is to fund the studies that give us a true insight into whether programs work or not. I don't know whether Dr. Alexander can—I have asked before and I will ask again whether you feel like there is adequate testing or research done, or if you all even have the capacity to do this of the programs that we are enacting in terms of what the results are, both short-term and over some amount of time.

Dr. ALEXANDER. Ms. Northup, some years ago when we entered the field of trying to assess the effectiveness of different education programs, particularly methods for teaching kids to read, we found a situation in which decisions on these programs were based on what books had pictures that were most appealing to kids, or what colors were used, and the research that was done was public acceptance or market appeal kinds of work rather than evaluations of the effectiveness of the programs in helping kids learn to read. These were the bases on which decisions were made about selecting textbooks, educational regimens, programs, whatever.

We have brought scientific rigor to this whole area of trying to assess effectiveness of educational programs. The success of this effort, which has not included everything that ought to be tested but some of the most important ones, was reflected, I think, in the passage of the President's legislation, the education bill that focused on not leaving any child behind. The bill requires that all reading instruction needed to be research-based and scientific in its approach and to be demonstrated to be effective if Federal dollars were going to be used to support it.

Our research continues. We also intend to be a resource to States and communities in trying to assess whether there is information to buttress their selection of these materials and how they are applied, but the President has asked us also to move beyond this to school readiness and how we can help children enter school maximally ready to learn.

So the research that we are starting this year and have requested dollars for in the 2003 budget focuses on the preschool area, relatively a new area for us in which we are looking at effectiveness of Head Start-type programs, how to bring cognitive efforts into the social and behavioral arenas that Head Start has focused on primarily in the past, how to do that most effectively, how to work in the community level, and at the home level to help par-

ents stimulate their child in the most effective ways to provide the readiness kinds of activities that will enhance the likelihood that that child will succeed when they get to kindergarten or first grade.

We are looking at different approaches that can be taken in these kinds of settings, again in a partnership, a collaboration with the Department of Education, with the Administration for Children and Families and HHS.

Mrs. NORTHUP. There would be some that would think we get things a little backward. First of all, we appropriate billions of new dollars for early childhood and getting kids ready, and then after the fact, we appropriate money for research, but I think it reflects a true concern on the part of us that we don't want to wait any longer for addressing young children's problems.

But Mr. Chairman, if I could just endorse that we provide all the funding we need so we get as good an insight as we possibly can as to what works, how it works best, what sort of intervention works because we are going to keep investing in early childhood. We are not going to give up on children, and in the meantime, to not have a guiding light is a big problem. I would like to also encourage you, though, to go beyond that and to establish some parameters for every single group that walks in your door, in my door, and says they are research-based.

If I could give one example, I think someone ought to write the tenet that you can't do your research on your own product, that if you develop a reading program that you then can't also do the research about whether it works. Somebody else has to and you see and you can understand this. Everybody wants to see research-based, but they do the research then they take a control group, a school, it might be their best school and do the research and show the gains, and then try to sort of sell that as repeatable strategy for addressing certain concerns, but there are others that as I listen to things, but that is the first one is that you can't research your own product, and it is just too subjective, and I can certainly think of some other scientific things but I feel that either there needs to be a good seal of approval, that there needs to be some sort of standards about what is research-based.

The other problem is, of course, that what you have now are some schools or some superintendents that actually pick up a program and if it were applied as it was meant to be applied, it might be research-based and successful, but they sort of pick and choose what they actually apply and then don't get the results that we are hoping for. But in any event, I think we all recognize that the promise to our children is primarily, or at least essentially an educational promise, and we need all the research we can get to give us better insights. I would be also very disappointed if we appropriated all this money to you all and you didn't give us very clear answers back, even if they are not always politically popular.

Dr. ALEXANDER. Ms. Northup, I certainly agree with your statements. Many programs, most programs claim that they are research-based. But the quality of that research is often lacking. For example, the National Reading Panel which the Congress directed us establish, indicated that less than 10 percent of the studies in the scientific literature were done up to quality standards such that they could be relied upon in terms of the validity of their re-

sults. So we had to throw out over 90 percent of the studies. And some of those were based on testing done by the sponsor, by the developer of those materials, but some were actually done by academics too. So it is important that we focus on the quality of the research and that judgments be made based on the quality of that work and not just that somebody claims it was based on some research.

Mrs. NORTHUP. Thank you. Thank you, Mr. Chairman.

Mr. REGULA. I have a couple questions and then I will get back to you Mr. Sherwood. Let me use Vioxx as an example. You see all the allegations of the good things it will do and then you read the little literature that is inside, and as to all these disclaimers, if you are over five feet tall, you shouldn't use this and on and on and on.

So I would like to have just one statement, this is approved by the NIH or it is not approved by NIH. I know you can't do it, but you see what I am getting at? How do you know where truth lies? You mentioned about what is effective all of this on your liver and spleen and other organs of your body. It makes you run but many of the trade-offs aren't worth it.

Mrs. NORTHUP. Yes.

ARTHRITIS MEDICATIONS

Mr. REGULA. Where do you go to get some degree of security.

Dr. KATZ. Mr. Chairman, let me respond, since you are talking about Vioxx, which is a COX–2 inhibitor, and there are several such drugs, but you can generalize to almost all of them. When you look up a drug in the Physicians Desk Reference, it lists the chemistry and the dosage of these drugs, you also list the contraindications; that is, if there are drug interactions. But also there is always a long list of potential side effects. Some of those are very, very, rare. Some of them are almost expected.

So as a physician, I would tell you that there is a physician's judgment that has to come into play in terms of balancing what you are treating with what the potential adverse effect is, and that is where physician's judgment comes in. We try to help that physician's judgment enormously.

Let us go back to what Ms. Northup talked about with regard to glucosamine and chondroitin sulphate. There are short-term studies that have shown that it is effective as you mentioned. As we are talking about collaborations here, I could tell you about a very good collaboration that has gone on for the last couple years between the National Center for Complementary and Alternative Medicine and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. These studies on glucosamine and chondroitin sulphate are looking at a longer term effect of that combination of alternative medicine. In addition from our standpoint at our Institute, we are interested in knowing whether it actually modifies the disease—whether it modifies this loss of the cushion between these joints—the same issue raised in your initial question about the injection of the Hyaluron.

So as a consequence, we are doing studies together, both contributing, both center and institute contributing to trying to get the answer in terms of disease modification. But to go back to the specific

question, it is a physician's judgment. There is no way that the NIH is going to say yes, you can use this or no, you can't, because there are these so-called side effects that are expected. And then there are what are called idiosyncratic side effects where some individuals, probably because of some genetic predisposition, which we will know about one day, react in an adverse way.

Mr. REGULA. So you roll the dice, you hope the benefits are going to far exceed the downside?

Dr. KATZ. I think as physicians we like to think that we are not rolling the dice, but we are making educated judgments with the patient's participation.

PLACEBO EFFECT

Mr. REGULA. A rose by any other name is a rose.

Dr. KIRSCHSTEIN. And balancing the benefits and the risks. For cancer drugs we take certain risks that we might not take for drugs for other diseases which are less fatal.

Mr. REGULA. Dr. Straus, the old Indian medicine man relied on the fact that as he went through all these gyrations, that the patient said I am going to get better. Do you think that is a factor?

Dr. STRAUS. Yes. The power of the mind to affect the body is a very real component in healing. We learn as children when our mothers comforted us that we are going to get better and we understand that expectation is followed by improvement. And we in the NCCAM are pursuing this very issue of how the mind and body communicate with each other in many ways. As an illustration, Mr. Chairman, in a partnership with 10 institutes this year, we have announced and will be funding next year, applications to understand the placebo effect.

This is exactly what you are discussing. We used to think this was just a sham that is in the mind, but in fact, we understand from recent studies that the expectation of getting better turns on certain centers of the brain and mediates that improvement. That phenomenon has been demonstrated very clearly in placebo benefit for pain disorders, and we at the NIH are using brain imaging technologies and molecular biology, to understand how this communication takes place so we can harness it and find better ways of assisting that expectation and process of self-healing.

Mr. REGULA. It is a very interesting observation and yet alternative medicine has, to some degree, be predicated on this placebo effect. I read the other day that in some of these tests, that people on the placebo were getting the same benefit as those taking the drug.

Dr. STRAUS. This is true of all medicine. Good research today, when it can include a placebo control arm does, because there is a certain rate at which any research subject will improve. There are two articles about this issue in tomorrow's Journal of the American Medical Association. The placebo effect is so great in certain kinds of conditions that it is occasionally difficult to prove that new drugs are superior to it—if we could just package the placebo.

Mr. REGULA. Interesting. Dr. Keusch, have you done any study on the correlation between Health and Economic Development in a nation, the prosperity of a nation is tied to health?

Dr. KEUSCH. Yes, Mr. Regula. There is a lot of evidence that health, in using certain measures, for example, longevity is directly related to income, and this is true in the developed world as it is in the developing world. There seems to be a break point at about $10,000 per capita and the increment of improvement in longevity as a measure is very limited thereafter, but this is actually a very important concept as we look at the larger world that we live in and as we are trying to deal with issues of poverty and development and all of the antecedent of the kinds of events that we saw in September of last year.

The paradigm is changing, and we are trying to generate evidence for this that improved health results in greater productivity and economic development, and that translates into better life, better quality of life, and we hope political stability markets and a whole set of secondary gains that occur.

The Fogarty International Center with a number of our colleagues at the National Institutes of Health, and an offshoot of The World Bank, called the Global Development Network are now sponsoring a series of research projects between U.S. Institutions working in developing countries to examine this hypothesis in order to be able to convince a minister of finance to invest in health, because unlike in our country, the ministries of health don't have any money, whereas we are able to put a significant amount of resources into improving our Nation's health. This is probably one of the main reasons why the United States is where it is today globally as a power.

Mr. REGULA. Would you agree that perhaps the mantra "leave no child behind" should have a health component as well as an education component?

Dr. KEUSCH. They go hand in hand. If you are not well, you can't go to school, and if you are not healthy, you can't learn.

Mr. REGULA. Mr. Sherwood.

Mr. SHERWOOD. It has been my experience that chondroitin also works very good on draft horses.

Mr. REGULA. They can't read the fine print on the back.

Mr. SHERWOOD. And on your comments on placebos, I am reminded of the story of my uncle Don, who was a dairy farmer and had 50 or 60 high producing dairy cows over a 50-year period, 45-year period. So he had a couple thousand dairy cattle over this period of time, that he knew every one by name and attended to their health and care with great precision. And he said over his 40 years, his favorite veterinarian was Dr. John Gashian, because when John came out to the farm, you felt better, even if the cow died.

GLOBAL HEALTH THREATS

Dr. Keusch, in the Fogarty International Center, since September 11, we are all very concerned with terrorism and bioterrorism and global health, but we have long known infectious diseases can be, to a certain degree, contained by political boundaries, and is your center involved in global tracking of health threats to us and how do you report potential threats to American public health from foreign nationals coming here or Americans traveling abroad?

Dr. KEUSCH. Well, you say that some diseases respect borders, but I know that mosquitos do not in transmitting malaria, and we have certainly seen the movement of infectious disease agents around the world through the rapid transportation systems that we have available. The Center and the NIH is not involved in surveillance from that perspective. We are involved in obviously studying the epidemiology and the movement of disease in order to be able to better define interventions. There are global systems to track disease in the context in which I think you have raised it.

Our job is to better understand the mechanisms in order to be able to devise interventions and carrying that back into the mechanisms of disease in order to develop both new drugs and new vaccines and their implementation. We need to understand how these diseases track in order to effectively intervene, and that certainly is an important research question using a whole range of tools including imaging, satellite imaging, and the use of mathematical modeling. So there is a whole range of activities that the Center and our colleagues at the National Institute of Allergy and Infectious Disease, child health, general medical sciences and others are engaged in.

Mr. SHERWOOD. Thank you. Dr. Kirschstein, and Mr. Chairman, this has been very informative, and if I was a little smarter, I would ask some for more questions, but I think I am okay for today. Thank you.

Mr. REGULA. You have been doing very well.

I do have a couple more, and that is, I note that our budget has $49 million, to do research in collaboration with the Defense Department, and it would seem that this would be a productive situation because you have somewhat of a controlled group if you are doing a study of an impact on a group of military people. Are you involved? Is it working out? Does this provide a pretty effective way of doing certain types of research?

Dr. KIRSCHSTEIN. Among the groups that we collaborate with is the Defense Department. The particular funds that you are talking about occur in three areas: The major area where there is collaboration going on is being used for a study of AIDS vaccine with the army in Thailand, and that is being done very specifically by National Institute of Allergy and Infectious Diseases. Both the military and that Institute have been studying varying candidate vaccines for AIDS for some time under different circumstances. The Army is particularly interested in using the vaccine in countries such as Thailand where our soldiers are at risk, and we are interested in both developing countries, as Dr. Keusch has described, as well as in the United States, and they are going to combine efforts in this regard. Some of the other funds are for research activities that are related to some of the things we do within the institutes, and this will be a matter of providing sustenance for some of the programs that the Army can no longer provide funds for, and we will do so.

Mr. REGULA. So you would say this is a money well spent, the 49 million?

Dr. KIRSCHSTEIN. It will be in the future, I am sure.

SHARING KNOWLEDGE GLOBALLY

Mr. REGULA. One last question. Do you get information from around the world? In other words, are there other parts of the world where activities similar to what you are doing are happening and that you can share with them, or are we pretty much the world's resource on the kind of work you are doing here?

Dr. KIRSCHSTEIN. As Dr. Keusch said, research is international, and he can elaborate on this.

Dr. KEUSCH. We certainly have—and this is across the whole of the NIH, great connections with the other major supporters of research. For example, in the United Kingdom the Medical Research Council and the Wellcome Trust, the Pasteur Institute, and there is a constant exchange of information, of planning, of thinking, of interaction in many of the disease areas. A number of institutes and institute directors have been involved with the World Health Organization. I am currently serving on the Advisory Committee on Health Research to the director general of——

Mr. REGULA. Could I interrupt you? What does a World Health Organization do? How does a World Health Organization affect Ralph Regula, for example, what exactly is the value of this? I have been thinking about whether there would be a value—and maybe you can answer this, take the Subcommittee, where is it, Switzerland?

Dr. KEUSCH. In Geneva.

Mr. REGULA. To meet with these people, is there a value in that?

Dr. KEUSCH. I think there is absolutely value. You don't have to go to Geneva to get a sense of what these international organizations are doing. Just down the road from here is the Pan American Health Organization and the Pan American Health Organization has been, for example, exceedingly effective in eradicating measles and polio from the Americas that has a direct impact on Mr. Regula, if you are traveling or your children are traveling to those parts of the world.

The difference between an organization like the National Institutes of Health, which is looking at the health issues from the perspective of science, and the World Health Organization is that it purports to—I don't know how many institutes and centers we have at the National Institutes of Health, and I don't know how many countries there are in the world right now, because there are increasing numbers of countries, but for the 190 countries, they must respond to each one of those and it makes it sometimes a bit difficult to focus in on what is absolutely necessary to do. I think as some of the discussion this afternoon, a science-based agency such as the NIH, can really address the scientific issues, as for example, Dr. Straus has been talking about in complementary and alternative medicine.

Mr. REGULA. Does the World Health Organization just assemble information to disseminate to its members, or does it do some types of research, or does it compare research in the U.K. versus what is being done in the U.S.?

Dr. KEUSCH. It does all of that. It addresses the needs throughout the whole developing world as well as the industrialized world. It makes recommendations. It pulls together expert committees.

Many people from the National Institutes of Health serve on those committees. I would be delighted at some point, if you would like, to spend a little more time and tell you more about what WHO does and how the NIH interacts with that organization, because we do have a good interaction.

Mr. REGULA. You think it is a very useful organization? Is it financed by contributions from various countries?

Dr. KIRSCHSTEIN. It is basically the equivalent on the health level to the United Nations.

Dr. KEUSCH. Yes. And I think it is a useful organization. I think it has limitations as well and we try to maximize the good parts of it and deal with the rest.

Mr. REGULA. Do other countries draw on your knowledge and your research to improve their health internally?

Dr. KEUSCH. Absolutely. Every week there are delegations from ministries of health and science and technology visiting the National Institutes of Health, and those visits are productive not only for them, but also for us as well.

Dr. KIRSCHSTEIN. In addition, Mr. Chairman, I think one of the very important functions we serve both at our academic health centers as well as within our intramural program, because we are the premier science organization of the country, is to be the training ground throughout the country where there are pockets of expertise in various fields for scientists from all over the world who come here to study and learn, many of whom, almost all of whom hopefully will go back to their countries and set up programs.

And in addition, Dr. Keusch and Dr. Ruffin can expand for you on programs where we send our scientists abroad. Now, that used to be much more prevalent back in the 1930's and 1940's, and right after World War II, it was quite prevalent for us to send scientists abroad to learn. We have become much more preeminent and the traffic goes much more the other way.

Mr. REGULA. Very interesting. Mr. Sherwood, no more? Well, thank you all. It has been a productive hearing. There is a lot more we can ask. We will have questions for the record, but it sounds to me like you are doing the Lord's work out there, and we take our health for granted in so many different ways. It is reflected, I guess, in the ever-growing longevity of people. The average age of individuals in the United States is going up in terms of death, and in some countries, particularly Russia, are going the other way. Just an aside, do we have much interaction with Russia? They seem to have some good science over there.

Dr. KIRSCHSTEIN. We have a great deal. We used to have a great deal more with the Soviet Union. We had all sorts of inter-institute agreements, particularly in heart disease, and in cancer. This became less the thing to do as our relationships generally with the Soviet Union got more difficult, and we are trying to build these up again with the various individual countries that made up the Soviet Union.

Again, Dr. Keusch, if you wish, can expand on that. The State Department has a program that is involved in that and we are relying on those scientists from Russia in particular who have ended up in this country who have some knowledge of what has been done in the field of organisms for bioterrorism as to what they

know. Dr. Fauci, who is coming down on, I believe, May 8, for a hearing on bioterrorism, may well be able to expand on that for you.

Mr. REGULA. Very interesting. Thank you all for coming.

Dr. KEUSCH. Mr. Regula, we can provide you with some information on our activities across the NIH with the Soviet Union, if you would like it.

Mr. REGULA. I would be interested. Thank you very much. Hearing is adjourned.

[The information follows:]

Activities With Russia

NIH collaboration with Soviet, and later Russian, research institutes, dates back to the early 1970s. Most of the collaborative activities have been between U.S. universities and counterparts within the Russian Academy of Medical Sciences, the Russian Academy of Sciences, or the Russian Ministry of Health. Initially, collaborations focused on topics such as influenza and cardiovascular disease, and were conducted on a cost-shared basis. After the collapse of the Soviet Union, joint work was conducted under the auspices of the U.S.-Russia Commission on Economic and Technological Cooperation. In more recent years, cooperative work has been expanded through partnerships with the U.S. Civilian Research and Development Foundation (CRDF). Throughout the decades of collaboration, joint research projects have been supported through the standard NIH peer-review process and the resulting science has been top-notch.

In FY 2000, NIH support for research and research training activities involving Russia amounted to approximately $6.5 million. Of this amount, over half supported 126 visiting Russian scientists at NIH intramural laboratories, and joint awards and training programs accounted for the remainder.

Examples of ongoing areas of endeavor include the HIV Prevention Trials Network, a multi-country project to develop prevention methods for HIV/AIDS, including addressing high-risk behavior in youth; tuberculosis and other infectious diseases; environmental and occupational health; and population and health. NIH institutes and centers with major projects with Russia include the National Cancer Institute (NCI); National Institute of Allergy and Infectious Diseases (NIAID); National Heart, Lung, and Blood Institute (NHLBI); National Institute of Mental Health (NIMH); National Institute on Alcohol Abuse and Alcoholism (NIAAA); and the Fogarty International Center (FIC). FIC is helping to build research capacity in the biomedical and behavioral sciences in Russia by supporting, through U.S. universities and non-profit research institutions, training for Russian health scientists and clinicians in epidemiology, prevention, and clinical research.

Since FY 1996, NIH has invested approximately $5.7 million in CRDF to support joint research projects in the biomedical and behavioral sciences with scientists from all countries of the Former Soviet Union (FSU). Projects are in the fields of virology, immunology, neurology, oncology, epidemiology, environmental health, physiology and biochemistry, microbiology, and biotechnology. In the latest round of competition of its Cooperative Grants Program for 2001-2002, 22 out of a total of 37 CRDF biomedical projects involved partners from Russia.

NIH COLLABORATIONS

Mr. Regula: All Institutes and Centers are involved in at least one trans-NIH project. How are these projects initiated?

Dr. Kirschstein: There are a number of ways trans-NIH initiatives are launched. Most frequently, these are driven by a common scientific interest which serves as an essential "glue" to bind and sustain such activities . For example, there is currently a trans-NIH mouse genome initiative that began as a direct outcome of a mouse genome conference convened by the NIH. This activity involves representatives from nearly all Institutes and Centers (ICs) and the group meets regularly to discuss program issues, program announcements or Requests for Applications. Many of these involve financial support by multiple ICs.

The NIH has also implemented trans-NIH activities as a result of congressional interest. For example, the Clinical Research Enhancement Act authorized that the NIH supports a clinical research curriculum award (K30). This program was launched with multiple IC participation, although a single IC is designated to administer the program.

Finally, there are trans-NIH programs that are implemented as a result of executive decision by NIH Directors. An example is the T15 program, short course in research ethics. This program is supported by multiple ICs to address the need for increased understanding and appreciation of research ethics.

Mr. Regula: Are Institutes and Centers able to enter into collaborations, either intramurally or extramurally easily or does the structure of NIH make some collaborations difficult to begin?

Dr. Kirschstein: Collaborations are commonplace and encouraged, between intramural scientists, between extramural scientists, and between intramural and extramural scientists. In fact, today's scientific endeavors more often than not require extensive collaborations due to their complexity and multidisciplinarity. Within the NIH intramural community, there are quite literally no boundaries between the Institutes' scientists. Very often, scientists working in the same building are from different Institutes, and a number of trans-NIH "research interest groups" have been established that are intended to cross institute organizational structure. In the extramural community as well, investigators commonly collaborate with one another and our grants policies anticipate and facilitate this collaboration. Additionally, Institutes have established a number of extramural programs that require cross-institutional collaborations. Finally, intramural investigators often form collaborations with extramural investigators. In fact, there are policies in place to facilitate participation of intramural scientists on extramural awards, although intra- and extramural funds are appropriately kept separate.

COLLABORATIVE RESEARCH WITH THE DEPARTMENT OF DEFENSE

Mr. Regula: The budget request directs $49 million toward collaborative research projects with the Department of Defense. Briefly describe these projects.

Dr. Kirschstein: In Fiscal Year 2003, NIH will fund the following DOD Medical research that is consistent with NIH's mission: (1) HIV/AIDS research; (2) research on the effects of medical technology, including radiation research treatment; and (3) medical free electron laser research, which could be used for medical diagnosis and therapy, and in particular, for the debridement of wounds.

Mr. Regula: These projects have been funded through the Department of Defense for several years. Why is the funding being shifted to NIH?

Dr. Kirschstein: These Department of Defense research programs are consistent with NIH's mission to support and conduct research to understand, treat, and prevent diseases that threaten millions of human lives. For many years, the NIH has supported and conducted research on diseases in collaboration with other government agencies. In all cases, the research conducted by DOD and NIH will be enhanced through a closer sharing of knowledge and research.

Mr. Regula: Who will conduct this research? Will DoD continue to conduct this research or will it be done through the NIH peer review process?

Dr. Kirschstein: The research will be a collaborative effort between NIAID and USAMRMC. During Fiscal Year 2003, NIAID will continue to fund and support operations of the current USAMRMC HIV Vaccine research program at the program's current location, including the Phase III HIV vaccine efficacy trial in Thailand that is scheduled to commence later in 2002. USAMRMC will be contributing expertise and the use of its infrastructure, in particular, its overseas labs, personnel, and host-nation contacts to support our common HIV research efforts.

As to the transfer of funds from NIDDK and NIGMS to DOD, the DOD will select research organizations or individual investigators to conduct this research.

These research projects will neither be advertised by the NIH, nor will the resulting applications be reviewed through the NIH review process.

Mr. Regula: Will the $49 million be transferred to DOD?

Dr. Kirschstein: NIH is working with DoD to finalize the details, but we anticipate that NIH and DoD will enter into interagency agreements to support these research projects.

HEALTH DISPARITIES

Mr. Regula: The racial and ethnic composition of the United States has changed dramatically over the last four decades. The 2000 Census collected information that allowed for 126 racial/ethnic categories. Do we need to enter into more collaborative endeavors with other countries to address health disparities?

Dr. Ruffin: While collaborative endeavors with other countries to address health disparities is an important area of consideration that is currently ongoing and will continue, the most immediate focus in this country is delayering the multiple factors that contribute to disparities in health status. Within that context, the early systematic efforts should focus on the regional and geographical disparities in health status within the United States, looking at the racial/ethnic populations living in such areas, and looking at the impact of culture, environment, and a related variation in biological expression on health status.

CENTERS OF EXCELLENCE

Mr. Regula: Many Institutes and Centers provide support for Centers of Excellence. Tell me more about these Centers and the impact they have on collaborations in research.

Dr. Kirschstein: More than half of the NIH Institutes and Centers (ICs) have supported Centers of Excellence over the past ten years. The guidelines for these Centers vary across the NIH and are designed to meet the research needs of the sponsoring ICs. For example, some Centers of Excellence require both basic and clinical research projects; others may require only basic research projects; and still others provide support only for core or shared resource activities. Centers of Excellence strive to enhance research collaboration by encouraging interactions among investigators who have not previously worked together or who are new to the particular area of research being solicited. All such Center applications undergo the standard NIH competitive peer review process that involves an initial peer review for scientific and technical merit followed by a second level review by a National Advisory Council. The NIH has recently asked the Institute of Medicine to review and assess Centers of Excellence supported by the NIH. We would be happy to make available to you a copy of their report when it has been completed.

NIAMS COMMUNITY HEALTH CENTER

Mr. Regula: Dr. Katz, your Institute opened a community health center in a medically under-served area of Washington, DC in July 2001. Tell me more about this initiative. Who operates the Center? What services are provided? What is the Institute's role in service delivery? How is the Center funded?

Dr. Katz: The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Community Health Center is a component of the Institute's newly established health disparities initiative, *The Health Partnership Program (HPP)*. As a research institution devoted to improving the Nation's health, the NIAMS recognized the lack of data regarding the basis, effects, and outcomes related to health disparities. The HPP was developed in collaboration with a wide range of community representatives and organizations to provide a platform from which such research could be done effectively and efficiently. The program is being piloted and currently concentrates on rheumatic diseases in the African American and Hispanic/Latino communities of the metropolitan Washington, D.C. area. Eventually, we will include other diseases within our mission and additional minority groups.

The HPP focuses on four key areas to address the multiple factors contributing to health disparities: *Public health education* focuses on disparities in awareness and information regarding the program's targeted diseases. *Patient care* emphasizes disparities in early detection and treatment and evaluates the role and impact of specialty care. *Access to clinical investigations* increases opportunities for underrepresented patient populations to participate in clinical studies of rheumatic and musculoskeletal diseases. *Recruitment to research careers* aims to increase the number of underrepresented minority investigators in biomedical research.

The health center has been established through a collaborative relationship with Unity Health Care, Inc., a nonprofit health care agency serving approximately 50,000 District residents with limited or no health insurance. It is located in the heart of the African American and Hispanic/Latino communities in Washington, D.C. The health center is operated by the NIAMS and serves as the primary site for the activities of the HPP at this time.

The health center serves as a platform for community-based research in health disparities. Currently one clinical research protocol, *Study of the Natural History of Rheumatic Disease in Minority Communities*, provides standard rheumatology care for enrolled subjects. This protocol provides for an investigation of the nature, severity, and outcomes of rheumatic disease among minority group patients. Information is collected as patients are interviewed and examined, undergo routine laboratory work and x rays for evaluation, and are treated and monitored for their condition. Patient education materials and classes are also offered. Health Center staff are available for presentations, continuing medical educational lectures, and other outreach activities in the public and professional communities.

The role of the Institute is to conduct research. Service is provided only within the context of clinical research protocols which are subject to institutional review for scientific merit and human subject protection. All patients must sign informed consent

documents detailing their voluntary participation in clinical research and their understanding that care is provided in this context. The role of the NIAMS in service delivery is to provide the staffing, support, and oversight for the clinic, as we do for NIAMS clinical research protocols conducted at the Bethesda campus of the NIH.

The NIAMS Community Health Center is funded through operating and program funds. The Institute's Intramural Research Program funds the operation of the clinic facility, staffing, supplies, upkeep, and daily activities. The Institute's Office of the Director funds the educational materials, outreach activities, and staffing related to these projects. The NIH Warren Grant Magnuson Clinical Center provides support for coordination of pharmacy, radiology, rehabilitation medicine, nutrition, and consultation services.

SHARED SCIENTIFIC KNOWLEDGE

Mr. Regula: Dr. Keusch, you have ongoing work in more than 90 nations. What countries are more advanced in their research endeavors? What have you learned from research in other countries that is used in this country today?

Dr. Keusch: Among the countries that FIC works with that are more advanced in their research endeavors are South Africa, Uganda, Brazil, Mexico, China, Thailand, India and Russia. These countries are among the most active participants in a number of FIC programs, for example, the AIDS International Training and Research Program, our Emerging Infectious Disease Program, our Maternal and Child Health Program, and our Environmental Health Program. FIC's efforts in many of these countries spans 15 or more years, and the impact of this investment is readily apparent when looking at advances made there in AIDS research and other fields.

Research conducted abroad--in both industrialized and resource-poor countries--adds to the foundation of scientific knowledge that leads to better understanding of the establishment and progression of disease and to the development of treatments and prevention measures. The U.S. benefits from research advances made worldwide since findings are published in the peer-reviewed literature and are available to all. Even resource-poor countries can make long-term commitments to participate in research, through collaboration with partners in industrialized countries. Such studies benefit the country where the research is conducted and communities around the world. The Institutes and Centers of the NIH advance research on global health challenges while preparing the next generation of scientists in the U.S. and overseas to conduct research. The Fogarty International Center supports international research and training programs, working closely with all the NIH components, to address health disparities worldwide. Following are illustrative examples of scientific research conducted abroad that have had major implications for health care in the U.S.

Research conducted in the developing world on AIDS and the virus that causes it, HIV, has contributed significantly to the body of knowledge concerning how the virus is transmitted and how the disease progresses, information that benefits the U.S. and the global community. For example, early in the AIDS epidemic when the rate of heterosexual transmission was low in the U.S., the rate was high in Africa. Information gained from transmission studies conducted in Africa helped U.S. scientists understand the risk factors and mechanisms of transmission and acquisition of infection. Another study in Uganda contributed to the body of knowledge used to establish the standard of treatment in the U.S. to prevent mother-to-child transmission of HIV. Large-scale studies conducted in Thailand with military groups and with commercial sex workers provided essential information on attitudes about the use of condoms, suggesting that effective use of condoms can have a major impact on the spread of HIV. By using new molecular technologies to identify the types of HIV that predominate in specific parts of the world, the US is able to track the spread of the virus in U.S. populations. Since AIDS is a global epidemic, only a global approach can be successful in halting its spread. Development of a safe and effective HIV vaccine remains essential for the ' global control of the epidemic. Once a promising vaccine candidate becomes available, it will be critical to test it for effectiveness in populations with a high incidence of HIV infection, both inside and outside of the U.S., and preparation for large-scale field-testing must begin now. Studies must be conducted at potential sites to establish HIV incidence, characterize potential populations for participation in clinical trials, and develop strategies for recruitment of study participants. Essential to preparation for large-scale vaccine trials is development of research infrastructure in resource-poor areas of the world that may serve as trial sites, including the training of individuals at those sites on how to conduct trials in an ethical and scientifically valid manner. Through FIC-supported training programs, NIH supports programs to prepare for the eventual testing of HIV vaccines and other interventions.

Advances made abroad on other infectious diseases have led to major improvements in health for the people of the U.S. as well:

- Studies conducted in Bangladesh on cholera, a severe diarrheal disease, led to the discovery that rehydration of patients with a solution of water and salts reduced the mortality from cholera from 50% to 1%. This seminal finding paved the way for the development of rehydration treatment for less severe forms of diarrhea that impact a range of groups, including infants and the elderly in the U.S. and around the world.

- The first field tests of the Sabin vaccine, which is used today in the U.S. for the prevention of polio, were originally done in Russia and Brazil.

- Collaborative international research has correlated a series of dengue outbreaks in Brazil with data on the density of the population of mosquitos that transports the dengue virus. This has provided U.S. public health officials with information regarding the dynamic of disease transmission and has helped inform policies to

prevent and control dengue infections for those at risk who live in U.S.- Mexican border communities. To demonstrate how one area of scientific endeavor often leads to unexpected benefits in other areas, collaborative work in Nicaragua to develop novel, simple, and low-cost molecular diagnostic tools to detect sub-types of the dengue virus has been translated into use for sub-typing strains of two other serious infections common in the U.S. One of these is a strain of E.Coli (0157H7), a common cause of food poisoning resulting from the ingestion of uncooked hamburger, the other being the virus that causes hepatitis C.

- A diagnostic tool developed in Brazil to detect leptospirosis, an emerging infectious disease, was recently used by physicians at the CDC and the Illinois Department of Health to detect new cases of leptospirosis in that state.

- With the explosion of tuberculosis (TB) cases worldwide, and multi-drug resistant forms in particular, it is critical to conduct ongoing studies to identify new strains of the bacterium that cause TB, and to train scientists working in this area globally as we monitor the spread of the disease in U.S. populations and develop appropriate treatments and prevention measures.

Advances in the field of genetics, through partnerships between U.S. scientists and those in developed and developing countries, have led to the physical mapping of the human genome. Additionally, international cooperation has made possible the identification of genes for cystic fibrosis, hereditary forms of colon cancer and breast cancer, hemoglobin disorders such as thalassemia, and movement disorders such as Huntington's chorea. Ongoing international research will shed light on how the interaction between genetic predisposition of populations and the environment causes disease.

Advances in our understanding of the normal development of the brain, the impact of toxins on brain development and our understanding of dementias has benefitted from research conducted abroad. For example, knowledge of the impact of maternal consumption of alcohol on brain development in-utero has been enhanced by major studies conducted in South Africa, where the incidence of the fetal alcohol syndrome is particularly high. This information has contributed to intervention strategies for the fetal alcohol syndrome, which is entirely preventable. Nobel prize winning work conducted in Papua New Guinea provided critical insights into transmissible factors that cause the development of dementia many years, even decades, later. This groundbreaking work served as an important early underpinning of numerous studies that have shed light on dementias that affect older Americans including those of Alzheimer's and Creutzfeld-Jacob Disease.

HUMAN GENOME SEQUENCING

Mr. Regula: Dr. Alexander, the mission of your Institute is to ensure, through research, the birth of health infants and the opportunity for each to reach full potential in adulthood. What impact will sequencing the human genome have on the mission of your Institute? Do you envision significant changes to the mission?

Dr. Alexander: The NICHD's mission is to help ensure, through research, that babies are born healthy and grow to become healthy adults. The sequencing of the human genome will allow NICHD researchers to focus, more precisely, on how genes contribute to healthy development. In addition, the Human Genome Project will enable researchers to conduct studies in the directions highlighted in the Institute's recent strategic plans. For instance, NICHD-supported researchers will focus on gene sequences associated with hereditary conditions and birth defects, eventually enabling researchers to develop treatments that optimize children's health. Moreover, sequencing the human genome will help researchers determine the links between behavior and gene expression, which will clarify how genes and the environment affect human health. Finally, the Human Genome Project will assist NICHD-supported researchers to identify genes that might influence an infant's risk for SIDS, which could help prevent thousands of infant deaths per year. Thus, the sequencing of the human genome will foster opportunities for basic and clinical scientists to collaborate and continue to carry out the NICHD's mission.

We do not envision that the mission of the NICHD will be substantially changed by the scientific achievement of sequencing the human genome. The new knowledge derived from the sequenced human genome, however, will provide extraordinary tools and resources that are likely to make it possible for the NICHD to reach some of its goals more rapidly and with greater effectiveness.

PPRU NETWORK

Mr. Regula: The Pediatric Pharmacology Research Unit Network, created in 1994, is a partnership among NIH, the pharmaceutical industry, and scientists at research and academic institutions. Tell me more about this network. How did it get started? What role does each entity have in its operation? What has been accomplished through the network? Is this a model that could or should be adopted by other Institutes?

Dr. Alexander: In 1990, the Institute of Medicine sponsored a workshop to address the issue of the lack of pediatric labeling. A major concern at the time of the workshop was the feasibility of performing drug-labeling studies in children. To address this concern it was recommended that the NICHD provide the infrastructure for collaborative efforts of pediatric pharmacologists to conduct clinical trials of drugs in children. In response, NICHD created a network of Pedicatric Pharmacology Research Units (PPRU) at seven academic institutions to demonstrate that such studies could be ethically and efficiently performed in children. In the ensuing years the network successfully performed over 100 studies in newborns, children and adolescents.

These efforts have been recognized by the Congress and the Pharmaceutical Research and Manufacturers Association. The network was expanded in 1999 to 13 units.

The PPRU Network, which is supported under the U01 cooperative agreement funding mechanism, constitutes a dynamic, integrated arrangement between NICHD and the grantees, making them equal partners in the common goal of insuring that drugs given to children are safe and effective. Other Institutes at NIH also have substantial scientific/programming involvement that includes facilitating the partnership within both the NIH and private industry. These partnerships help to balance the project's activities with new and emerging drug research opportunities in children.

It is important to note that none of NICHD's appropriated funds are used to support clinical/technical costs (i.e. patient-related costs) associated with the performance of a given trial. Rather, these costs are borne either by the phamaceutical sponsor or are from other extramural resources.

The PPRU Network has provided the pharmaceutical industry with a critical niche in the process of drug development for infants, children and adolescents. PPRU investigators are experts in designing pharmacokinetic and/or pharmacodynamic studies focusing on children. They design, or help sponsors to design, clinical trials that minimize discomfort in children and disruption in the children's family life.

From its inception, researchers at the PPRU network have been involved in characterizing changes in drug metabolizing enzyme activities that occur as children mature. Pharmaceutical companies have joined in this research effort by permitting ancillary studies as part of their protocols.

Prior to the Food and Drug Administration Modernization Act of 1997 (FDAMA), the PPRU Network performed 17 industry-sponsored protocols. The first year after FDAMA was enacted, 21 protocols were active in the network. In 1999, 54 industry-sponsored protocols were active, a 200% increase over pre-FDAMA activity. In 2001, the number of active protocols increased to 85. This remarkable growth in pediatric clinical trials within the network reflects the overall increase in pediatric drug development during the first two years of FDAMA.

PPRU studies have included pediatric subjects who are well-distributed by age to provide information across the entire developmental spectrum . In contrast to the pre-FDAMA era, more of the protocols today are targeted to early phase studies in children with an emphasis on pharmacokinetic/pharmacodynamic studies, which are important to understanding the developmental differences in drug response.

It should be emphasized that 66 percent of the network studies involve new molecular entities in pediatrics. These studies are not covered by FDAMA. The network studies have focused on a variety of new compounds including plecoranil, the

first agent effective in the treatment of enteroviral meningitis in infants, a leukotriene antagonist for the treatment of asthma, pentoxifylline for the treatment of Kawasaki disease, a new D2 receptor antagonist for conduct disorders, a new triazol for systemic fungal infections, inhaled insulin for the treatment of Type 1 diabetes, and the first liposomal nystatin formulation in pediatrics for the treatment of fungal infections.

Not only is the PPRU Network a model which can be adopted by other Institutes, it has already been applied in the development of the NIMH Research Units in Psychopharmacology. The application of the new techniques of biology to drug development in pediatrics and consequent development of drugs directed to affect molecular targets will increase the usage of "specialized" networks.

NCCAM INTERNATIONAL HEALTH ACTIVITIES

Mr. Regula: Dr. Straus, many cultures have a tradition of incorporating herbs and/or other therapies into their healing practices. Have other countries done any studies to prove the efficacy of these medicines and therapies? What are you doing to collaborate with research conducted in other countries?

Dr Straus: Many complementary and alternative (CAM) practices have originated in other countries. Studies to determine the efficacy and safety of these practices have been conducted by investigators in a number of countries, primarily in Western Europe. Like many of the earlier studies of CAM conducted in the U.S. to date, there has been great variability in scientific rigor

NCCAM supports a variety of international activities, including scientific workshops, training programs, and research projects. In 2001, NCCAM sponsored a workshop on clinical research methodology and grantsmanship in Singapore. The Center also supports an ongoing international bioethics training program in a partnership with the Fogarty International Center. NCCAM is supporting the work of investigators at the University of British Columbia who are studying the rational and safe use of nutraceutical products. In Fiscal Year 2003, NCCAM is planning to solicit applications to develop an international site of CAM research excellence. The purpose of the program would be to conduct studies and train new investigators. NCCAM recognizes that a global network of rigorous CAM researchers will also enhance CAM research activities in the United States.

EARLY CHILDHOOD DEVELOPMENT

Mrs. Northup: Last summer the White House convened a summit on early childhood cognitive development and more recently the President has made several proposals regarding early childhood education. What has your research shown about the pre-literacy skills that are necessary so that a child goes to school ready to learn?

Dr. Alexander: For the past ten years, NICHD has focused on identifying procedures for detecting children at risk for reading failure during the preschool through kindergarten years, with subsequent evaluation of the effectiveness of a small number of early childhood early literacy intervention programs. Most of this work has focused on older children. However, NICHD-supported scientists at Florida State University have found evidence clearly indicating that preschool children (ages 3 to 4 years) who are at risk for reading failure can be reliably identified. In addition, several abilities have been found to be associated with early reading achievement, including language ability, phonological awareness, concepts of print and letter naming. Results of the analyses carried out by the National Reading Panel indicated that children in preschool can acquire phonological and letter-sound concepts quite adeptly if these concepts are presented in a systematic and explicit manner.

None of these studies consist of research designs that can address the specific question of which pre-literacy skills are necessary for children to develop while they are preschoolers that will better prepare them to benefit from formal schooling. Therefore, the NICHD will be collaborating with other agencies across the DHHS and the U.S. Department of Education to fund experiments to address this question in the context of a broader Interagency Early Childhood Research Initiative. One purpose of that initiative is to identify the pre-literacy components of comprehensive early childhood education programs, such as Head Start, that are essential to early reading and school achievement.

Mrs. Northup: Have you conducted any research regarding the Head Start program and how it could incorporate educational components into its programs?

Dr. Alexander: The NICHD has not previously funded research that can address this question, nor is rigorous scientific evidence available that can specify the essential curriculum content, program components, and associated teacher preparation needed to comprehensively prepare diverse populations of children for early school success. Therefore, the NICHD is collaborating with the Administration for Children and Families, the Office of Special Education and Rehabilitative Services in the Department of Education, and other DHHS agencies on a $45 million, 5-year research initiative to begin filling this gap in knowledge. This initiative will stimulate rigorous experiments to identify how best to promote children's emerging literacy, language, and cognitive development while also supporting their social-emotional competency, self-regulatory skills, positive dispositions toward learning, and physical health. In this context, the initiative encourages a focus on the early detection and prevention of learning disabilities, challenging behaviors, and emotional problems that affect school transition

and achievement. Scientists will be encouraged to establish partnerships with early childhood programs that include Head Start and Early Head Start as well as pre-kindergarten programs, center-based child-care, and family day care. The initiative has begun with a $2.5 million solicitation to support essential start-up activities in FY 2002 for large-scale multiple-site studies to be funded in FY 2003. The NIMH and the DHHS Office of the Assistant Secretary for Planning and Evaluation are co-funding the initiative in FY 2002.

Mrs. Northup: What has your research shown about the criteria needed so that we can determine whether or not early childhood education programs are teaching children needed skills?

Dr. Alexander: The NICHD has not previously funded research that identifies specific criteria and associated measures needed to assess whether or not early childhood education programs effectively promote the knowledge, skills, and dispositions associated with children's early reading and school achievement. However, this work is an essential component of the Interagency Early Childhood Research Initiative. The NICHD will be sponsoring a workshop in June 2002 in collaboration with the ACF/ACYF/Head Start Bureau and the Office of the Assistant Secretary for Planning and Evaluation. The purposes of the workshop are to: (1) identify essential outcomes in each area associated with school readiness that are essential from birth through age five in order to evaluate children's progress; (2) identify what is known about how to measure learning and development in each individual child in reliable and valid ways; (3) identify gaps in measurement that currently exist; and (4) establish priorities for addressing these gaps through research.

Scientists funded through the Interagency Early Childhood Research Initiative will use these recommendations to select assessment criteria and measures that are most appropriate for identifying which components of comprehensive early childhood programs effectively promote children's progress in areas such as literacy and language, and their early achievement in kindergarten and first grade.

READING SKILLS IN OLDER CHILDREN

Mrs. Northup: For several years I have been interested in what we can do to help older children who have slipped through the cracks and are not successful readers. Unfortunately, this is a difficult population to address. I know that this past fall you were scheduled to have a workshop on adolescent literacy. Were you able to identify where the gaps are in the scientific research regarding older children and reading?

Dr. Alexander: The NICHD has already held one workshop in March 2002, and is planning another for mid-May, on the important topic of adolescent literacy. These workshops have been cosponsored by the US Department of Education's Offices of Vocational and Adult Education, Elementary and Secondary Education, Special Education and Rehabilitation Services, and Educational Research and Improvement, as

well as four major professional associations: the American Federation of Teachers, the American Speech-Language-Hearing Association, the International Reading Association and the National Education Association. The summary document from the first workshop and a draft research agenda are in process at present and will be posted on the various organization web sites in time for the May workshop. The major areas of research discussed include detailed, rigorously designed studies of instructional methods used with middle and high school students, and longitudinal studies of the developmental learning trajectories of students in this age span. Studies must take into account learner characteristics and teacher preparation. There is a lack of knowledge in fully understanding the role of the major components of reading (phonological awareness, fluency and comprehension) in students in middle and high school. Additionally, we know that student motivation is a major factor in learning to read, especially in students who may have experienced failure for a period of years. We need to understand how best to motivate students and sustain that motivation as we provide high quality instruction to them. Finally, we must understand the neurobiological factors that interact with learning in adolescents, in order to improve both instruction and intervention.

Mrs. Northup: What sort of guidelines have you put out for the direction of future research on this population?

Dr. Alexander: The draft research agenda that is being produced from the March 2002 workshop on adolescent literacy will be refined in the upcoming May 2002 workshop. The NICHD anticipates funding research to address the priorities identified by these workshops in Fiscal Years 2003 or 2004, in cooperation with the US Department of Education. The guidelines for any such solicitation will be drawn directly from this final research agenda.

POST NATIONAL READING PANEL

Mrs. Northup: For several years now we have known how children learn to read. With the release of National Reading Panel we know that there is converging evidence of the scientific research on how children best learn to read. Now that we know that, what is the next step? In what direction is research on how children learn to read headed? Now that we know what we know, how do we build upon that investment and what questions are still left unanswered?

Dr. Alexander: The NICHD, both independently and in collaboration with the US Department of Education and the National Institute for Literacy, has expended major efforts in disseminating the findings of the National Reading Panel and the implications of those findings for classroom practice. The National Institute for Literacy (NIFL), in collaboration with the Department of Education and the NICHD, has created the Partnership for Reading, a national reading dissemination project authorized by the No Child Left Behind Act of 2001. This partnership has a mission to make scientifically-based reading research more accessible to educators, parents, policymakers, and other

interested individuals. An example of this are the *Put Reading First* booklets, which have taken the NRP findings and translated them into instructional strategies and literacy activities that can be used by teachers and parents. The *Put Reading First* teachers' guide and parent brochure have been very widely disseminated and have been highlighted as a tool for teachers. The next steps include ongoing research and various new initiatives in reading and literacy.

The NICHD continues to fund research on the psychology and neurobiology of reading and reading disabilities, reading fluency and comprehension, and English reading in Spanish-speaking children. In FY 2002 the NICHD will also fund projects addressing adult and family literacy, as well as planning grants on early literacy and school readiness. In addition, the NICHD continues to partner with the National Science Foundation and the Office of Educational Research and Improvement on the Interagency Educational Research Initiative to fund research on how best to implement effective educational interventions in the key areas of reading, science, and mathematics.

Now that we know children in kindergarten through the early grades need systematic instruction in the major components of reading (phonemic awareness, phonics, reading fluency, vocabulary, and comprehension), we could extend the knowledge of effective instruction to other age groups - preschool, later grades, middle and high school and adulthood. More research could be done to more fully understand the neurobiology of reading, and to seek ways to close the gaps that exist for both non-English and English language populations at all ages, and to develop reading interventions that are effective for children with reading and other disabilities. The NICHD has been active in researching initiatives that will address these various areas.

AUTISM

Mrs. Northup: Based upon your experience with NIH's research on autism, have we made any real progress in this area? Do we know how and why it occurs?

Dr. Alexander: There has been a great deal of progress in autism research. Recent and ongoing research provides new ways to diagnose autism and autism spectrum disorders at younger ages. These advances have led to more evidence that early intervention improves outcome. They have also facilitated studies assessing the efficacy of different forms of intervention. For example, despite initial enthusiasm for the therapeutic value of an expensive hormonal agent known as secretin, a carefully controlled clinical trial has provided convincing evidence that it is not an effective treatment for most individuals with autism.

Technological advances in neuroimaging have provided clues as to how individuals with autism perceive and process information. This is directly relevant to the social communication problems these individuals have. In addition, these new brain imaging techniques allow investigators to identify and study specific brain regions

related to specific learning and behavioral characteristics in autism. Better understanding of these brain-behavior associations can potentially lead to more effective behavioral or pharmacological interventions.

Progress is also being made in discovering candidate genes that may help explain specific features of autism. For example, it is now recognized that behaviors associated with autism are shared, to varying extent, with other disorders with known genetic etiologies (e.g. Rett Syndrome and Fragile X syndrome). Study of these disorders may provide important clues to the underlying genetic basis of autistic features.

There is very strong evidence that there is an underlying genetic basis for autism. This comes from the study of autism in twins. In 60 percent of identical twin pairs who share the same genetic information, both individuals have autism. This is true only in about 3 to 6 percent of fraternal twins, who have only half their genetic material in common.

People diagnosed with autism can have a wide range of symptoms, with an equally wide range of severity. The complexity of autism and its range of manifestations suggest that no single gene is responsible for the development of all cases and all features of autism. Studies of genes suspected to be associated with the characteristic findings in autism show that no one of these is found in all individuals diagnosed with autism. At present, it is thought that autism is the result of many genes interacting with each other, and possibly with environmental factors.

Mrs. Northup: How is information about autism disseminated?

Dr. Alexander: NICHD is committed to ensuring that the results of our research on autism are disseminated, quickly and accurately, to the professionals, parents and other individuals who can benefit from our research.

We have developed a series of fact sheets on autism, which summarize scientific information and present it in an easy-to- read and easy-to-understand format. The fact sheets include background on autism and the MMR vaccine, autism and genes, and a Q-A on autism for health care professionals. Six fact sheets are currently available and they will soon be available in Spanish. They are being promoted through announcements in national newspapers, magazines, and on radio and television programs.

The NICHD autism Web page, which is part of the NICHD Web site, is another primary way that we disseminate information about autism to the public. This site provides professionals, parents, and other interested parties with easy access to the most current information about NICHD research projects, publications, news releases and other activities related to autism. Many of our autism-related publications can be directly downloaded from the website. NICHD also disseminates information about autism through exhibits at conferences and meetings. Interested people who hear about our information can order material by calling a toll free number.

Mrs. Northup: Has NIH evaluated behavioral therapy, specifically Applied Behavioral Analysis as developed by Ivar Lovaas at UCLA, and what has it shown?

Dr. Alexander: The NIH has funded a number of research projects that have used applied behavior analysis, including a multisite project for which Dr. Lovaas was the principal investigator. Applied behavior analysis, which generally focuses on reducing specific problem behaviors and teaching new skills, may reduce the problem behaviors in some autistic individuals. Many other behavioral interventions have also been shown to be beneficial in some individuals, such as programs designed to increase positive behaviors and improve the individual's lifestyle. In addition, current projects that attempt to improve specific aspects of behavior, such as joint attention and imitation skills, show promise as treatment regimens. Individualized education programs that incorporate such approaches have been shown to be an effective way to prevent some problem behaviors typically related to autism for some individuals.

BONE DENSITY IN CHILDREN

Mrs. Northup: I am interested in your research regarding the high intensity jumping regimen that increases bone mass in children at the hip and the spine. Why is increasing peak bone mass in children so important?

Dr. Katz: NIAMS is supporting two research projects that investigate the effects of jumping on increasing the mass of growing bones. The first study seeks to evaluate bone mass of the lumbar spine and femur of 200 pre-pubescent girls and boys who are randomly assigned to a double-leg-jumping group or stretching control group. The second research project is investigating the effect of a jump rope and calcium intervention program in fourth-grade boys and girls and will be examining bone density at the lumbar spine and femur as well as the total body.

Prevention of osteoporosis is dependent upon maximizing bone mass early in life and minimizing bone loss later in life. Bone mass accumulates during the childhood and adolescent years and stops when young adults are in their mid-20s. Peak bone mass at the completion of skeletal acquisition is sometimes referred to as the maximum bone bank, and is important in determining fracture risk. It is postulated that increasing bone mass 3-5 percent would reduce fracture risk by 20-30 percent. As a person ages (particularly women at the time of menopause), bone is lost from the bone bank. The more bone in the bank, the less impact bone loss has on the body. Therefore, it is important to achieve a healthy bone density or mass during the early years of life. Loading the skeleton through weight-bearing exercises may be an effective way to encourage the accumulation of bone mass. Animal studies have shown this to be true, and the hypothesis is now being tested in humans.

Mrs. Northup: What are the implications of this research on other studies regarding bone disease?

Dr. Katz: Low bone density (osteopenia), osteoporosis, and fractures are more likely to occur among children who have cancer, muscular dystrophy, cerebral palsy, or cystic fibrosis. Low bone density is also common among children who are being treated with corticosteroids for a rheumatic disease, such as juvenile systemic lupus erythematosus. The development of interventions to maximize bone growth and minimize bone loss among children with chronic diseases may prevent a deficit in bone density and subsequent fractures both during childhood and adulthood. For example, the NIAMS is currently funding a clinical study investigating the possible beneficial effects of bisphosphonates (drugs that are used to treat osteoporosis in menopausal women) for treating osteoporosis associated with several pediatric conditions.

MUSCULOSKELETAL AND SKIN DISORDERS

Mrs. Northup: So much of the medical research we hear about involves expensive drugs or surgical procedures. Can you tell me more about other research you have conducted that involves less invasive ways of addressing musculoskeletal and skin disorders?

Dr. Katz: Non- or minimally invasive diagnostic and treatment procedures are often associated with lower morbidity and reduced cost. To identify new research opportunities related to functional imaging of soft tissue – such as skeletal muscle, tendons, and ligaments – the National Institute of Arthritis and Musculoskeletal and Skin Dieases (NIAMS) recently organized a roundtable meeting with experts from NIH and the extramural community. Initiatives which are developed as a result of this meeting will build on projects already supported by the NIAMS to promote techniques that show promise of being comparable in effectiveness to invasive procedures, yet offer greater safety and economy.

Renal osteodystrophy (ROD) is a disorder noted for skeletal deformities and fractures. Knowledge of the underlying bone abnormalities is essential for selecting and monitoring treatment. To date, bone biopsy is the only means for characterizing ROD. NIAMS-supported researchers are investigating the use of a noninvasive "virtual bone biopsy" based on micro magnetic resonance imaging, which will help diagnosis and treatment. Other research projects to develop non-invasive diagnostic tools are focusing on osteoarthritis (OA), a degenerative joint disease. Currently, there is no reliable non-invasive method for detecting and evaluating the early stages of OA. Researchers funded by the NIAMS are investigating the use of sodium magnetic resonance imaging as a non-invasive means for detecting the early cartilage changes that signal the onset of OA. The NIAMS is also supporting a multi-center study of 1,450 patients to compare the effectiveness of non-surgical versus surgical treatment of back conditions involving a herniated (bulging) lumbar disc, spinal stenosis (narrowing of the canal through which the spinal cord passes), or degenerative spondylolisthesis, where a vertebra in the spine slips out of place.

With respect to skin diseases, more than 20 million people in the U.S. have atopic dermatitis or psoriasis. For severe disease, immune-suppressive drugs such as cyclosporin are administered. However, cyclosporin may affect kidney function or lead to high blood pressure. NIAMS is supporting research on a topical cyclosporin A medication that may prevent some of the systemic problems associated with this therapy.

ARTHRITIS

Mrs. Northup: Unfortunately, arthritis is a disease that affects so many Americans, even those that are not old. However, many of the prescription medicines that are commercially available, are also extremely expensive. What kind of alternative therapies are available to reduce arthritis pain?

Dr. Katz: The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is partnering with the National Center for Complementary and Alternative Medicine on the NIH Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT). This is the first multicenter clinical trial in the United States to test the effects of glucosamine and chondroitin, two natural substances found in and around cartilage cells, for the treatment of knee osteoarthritis (OA). Scientists are looking at whether these supplements reduce the pain and disability associated with knee OA, as well as whether they halt disease progression. Another alternative approach to arthritis pain is acupuncture, a traditional Chinese method of pain relief in which thin needles are inserted at specific points in the body. NIAMS-funded researchers are evaluating the use of acupuncture on patients with OA of the knee. Preliminary findings suggest that traditional Chinese acupuncture is both safe and effective as an additional therapy for OA, significantly reducing pain and improving physical function.

Mrs. Northup: What have we learned about preventing arthritis?

Dr. Katz: The NIAMS supports a broad range of arthritis research, including studies to identify risk factors and develop prevention strategies. Work on osteoarthritis (OA), a degenerative joint disease that is the most common type of arthritis, has revealed that maintaining a healthy body weight and engaging in moderate physical activity are two ways to reduce your chances of developing this condition. NIAMS-funded researchers found that people who do moderate, regular running have low, if any, risk of developing OA. Another study found that a relatively small increase in strength (20-25 percent) can lead to a 20-30 percent decrease in the chance of developing knee OA. In addition, scientists have learned that people who have had a previous joint injury are more likely to develop OA, underscoring the need for education about joint injury prevention and the proper use of sports equipment.

In other OA research, the NIAMS has partnered with the National Institute on Aging to spearhead the Osteoarthritis Initiative (OAI), a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of OA. Such biomarkers have the potential to lead to novel and more

effective ways to predict and monitor disease activity and responses to treatment. Over 5-7 years, the OAI will collect information on 5,000 people at high risk of having OA and of progressing to severe disease. Additionally, the Institute recently issued a research solicitation following a major conference on OA prevention. Very shortly several new research projects, totaling approximately $2 million, will be awarded focusing on the prevention of onset, progression, and disability of OA.

The NIAMS has also launched the Health Partnership Program to address health disparities that exist among minority groups for rheumatic, musculoskeletal, and skin diseases. Prevention, along with treatment, education, research and training, is a key aspect of this initiative, which includes a Community Health Center in an underserved area of Washington, D.C.

IMPORTANCE OF VITAMINS

Mrs. Northup: It seems that throughout many of your colleagues hearings, we have learned of the importance of vitamin E for warding off a host of diseases. What has your own research shown about the importance of this vitamin?

Dr. Straus: According to a recent report on Dietary Reference Intakes (2000) by the National Academy of Sciences, current dietary patterns appear to provide sufficient vitamin E to prevent deficiency symptoms and overt deficiency is very rare.. Some experimental evidence suggests that high intake of vitamin E may lower the risk of some chronic disease, especially heart disease. However, the limited and discordant clinical trial evidence available precludes recommendations at this time of these higher doses of vitamin E to reduce chronic disease risk. The Tolerable Upper Intake Level (UL) for adults is set at 1000 mg/day for any form of supplemental alpha-tocopherol (the active form of vitamin E), because higher doses than these can increase one's risk of bleeding. NIH currently has ongoing trials that are looking at the effects of vitamin E supplementation on prostate cancer, rate of cognitive/functional decline, and cardiovascular disease.

Mrs. Northup: Should all Americans take a multi-vitamin every day?

Dr. Straus: Because of NIDDK's research efforts in this area, I sought its advice in answering this question. The dietary recommendations of the USDA Food Guide Pyramid allow most people to meet their nutrient needs. However, according to the 2002 Dietary Guidelines for Americans (developed by DHHS and USDA), some people may need a vitamin or mineral supplement to meet specific nutrient needs. For example, women who could become pregnant are advised to eat foods fortified with folic acid or to take a folic acid supplement in addition to consuming folate-rich foods to reduce the risk of some serious birth defects. Older adults and people with little exposure to sunlight may need a vitamin D supplement. People who seldom eat dairy products or other rich sources of calcium need a calcium supplement, and people who

eat no animal foods need to take a vitamin B12 supplement. Health care providers may advise pregnant women to take an iron supplement and adults over age 50 to get their vitamin B12 from a supplement of from fortified foods.

Mrs. Northup: When we become ill, perhaps with just the common cold, where can we turn to learn the best information about what vitamins may be helpful to us?

Dr. Straus: We suggest going to the Website developed by the NIH Office of Dietary Supplements (ODS) (<http://dietary-supplements.info.nih.gov/>). You will find Fact Sheets on specific vitamins and minerals. These were developed by ODS and the NIH Clinical Center. You will also find the IBIDS (International Bibliographic Information on Dietary Supplements) database which allows you to perform keyword searches for information published for consumers and professionals.

ORIGINS OF RESEARCH

Mrs. Northup: Where do most of the ideas for alternative and complementary medicinal research come from? Are they from direct research into the properties of a plant or animal, or do they come from the customs of other cultures that may have historically used such products?

Dr. Straus: Ideas for research on complementary and alternative medical (CAM) therapies come from consumers, physicians, researchers, and CAM practitioners, as well as NCCAM staff and their colleagues in other NIH institutes. These diverse origins share a common foundation -- the relative popularity of a given therapy and the extent to which conventional scientific knowledge can leverage new insight into that therapy. For example, St. John's wort, reportedly one of the top selling botanical products, is a key priority for study by NCCAM. Our ability to launch a large Phase III clinical trial of this botanical, without several NIH-funded pilot studies, was greatly enhanced by the pre-existing body of evidence emanating from scientific research into its safety and efficacy. Conversely, although NCCAM supports studies in areas like energy healing, there is not yet sufficient evidence to demonstrate the usefulness of a large-scale randomized, controlled clinical trial. Thus, the first studies undertaken by NCCAM are careful pilot trials.

Insights into the safety and efficacy of complementary and alternative medical therapies come from a direct analysis of the purported healing substances, studies on the mechanisms by which such therapies might work, and the cultural context in which those therapies are practiced.

FORMS OF EXERCISE AND MEDITATION

Mrs. Northup: Much of your research has focused on botanical products used for therapy. Have you conducted any research into behavioral therapies for the treatment of diseases, such as different forms of exercise, like yoga, or meditation?

Dr. Straus: NCCAM currently supports a wide range of studies on therapies like yoga, meditation, tai chi, and Qigong, for several health disorders. For example, yoga is under study as a treatment for insomnia and asthma in pregnant women. Meditation is the therapy employed in research NCCAM funds on patients with hypertension and congestive heart disease, and to control binge-eating disorder. Qigong is being evaluated as an aid to improve the quality of life in cardiac patients with heart-assist devices. Tai chi is under study to reduce stress in people with HIV/AIDS, to improve immunity and health functioning in people with herpes zoster infection, and to assist in the sense of positional stability of people with inner ear disorders. In a study of people with Parkinson's disease, tai chi and qigong are being compared to conventional aerobic exercise to determine which provides better improvement in control of movements. The benefits of massage, tai chi, and meditation are being studied for their relaxation potential in a study of people with chronic back pain.

CONFLICTS WITH PHARMACEUTICALS

Mrs. Northup: What kind of information do you provide to the public to prevent the mixing of herbal supplements, like St. John's Wort, with traditional pharmaceutical medicines which can diminish their effectiveness?

Dr Straus: The National Center for Complementary and Alternative Medicine (NCCAM) web site has a special section entitled "Alerts and Advisories" (http://nccam.nih.gov/fcp/alerts/index.htm) where important consumer advisories and information on herb/drug interactions are posted. Current listings include information on kava, PC SPES, garlic, and complementary and alternative medicine for bioterrorism. The web page also includes a link to the Food and Drug Administration for additional information. In addition, fact sheets on herbals, such as St. John's wort, have information on herb/drug interactions. The public may also contact the NCCAM Clearinghouse by letter, phone, fax, or e-mail to get this information.

PPRU NETWORK

Mr. Obey: In your budget testimony you mention the Pediatric Pharmacology Research Unit. Please describe that program and its purposes. What are the scientific reasons for testing drugs for safety and effectiveness in children (rather than relying on the results of testing in adults)?

Dr. Alexander: The Pediatric Pharmacology Research Unit Network (PPRU) was created to achieve the following objectives:

- To provide a locus for the conduct of studies on bioavailability, formulations, drug metabolism, pharmacokinetics, pharmacodynamics, safety, and effectiveness of new drugs and drugs already on the market;

- To gather or promote the accrual of the necessary clinical data for pediatric age-specific labeling of drugs;

- To conduct research on new pediatric therapeutic modalities, including: a) molecular approaches to the treatment of diseases; b) application of new technology to pharmacodynamic studies and drug delivery systems; c) development of pediatric formulations; and d) validation of new endpoints or surrogate markers;

- To conduct studies on the developmental characteristics and genetic polymorphism of drug metabolizing enzymes, pharmacokinetic modeling, and simulation technology; and

- To provide a teaching environment in which pediatricians, pharmacists, nurses and others can gain supervised experience in pediatric clinical trials and training in evidence-based pediatric pharmacology.

A number of therapeutic mishaps have clearly shown that dosing derived from adult studies cannot be extrapolated to infants and children. For many drugs, developmental, metabolic, and pharmacokinetic-pharmacodynamic data is needed to determine their safe and effective use in children. The differences in the drug reactions are due to the maturational heterogeneity of children of different ages, their unique physiological and biochemical characteristics, unique diseases ,and therapeutic needs.

A major challenge is to close the gap in the lack of current knowledge regarding the ontogeny of drug metabolizing enzymes, drug transporters, and drug targets. The shift in the central pharmacologic paradigm from symptomatic relief to targeting the cause or mediators of disease processes makes acquisition of this knowledge a priority.

As a group, Phase II enzymes have not been well studied. Limited information suggests variable developmental patterns. An understanding of the role of drug transporters is fundamental for the characterization of drug disposition and the understanding of drug resistance in children.

There is little knowledge on the pharmacologic significance of various brain receptor assemblies during a child's development. The increased use of psychotropic and antipsychotic medications in children raises concerns about the short- and long-term effects in brain development. These drugs may cause a decrease in beta-adrenergic receptor functions, which may contribute to the severity of asthma. As of now, actual effects are still unknown.

There is also increasing evidence that the effects of dopamine are likely to influence response to therapy in cases of pediatric arrhythmia. The pathophysiology of convulsions and response to therapy is different in children, especially newborns, compared to adults. Studies are necessary to confirm this hypothesis since the mechanisms regulating the development of pediatric arrhythmia are still obscure.

In summary children are not miniature adults and there is a need to unravel the extent and significance of the differences between them. This objective can only be achieved by the interaction of clinical, translational and basic research scientists, a major concern of the PPRU Network and the NICHD's program in Developmental Pharmacology.

NCS

Mr. Obey: Please give us a report on the status of the National Children's Study of Environmental Influences on Health and Development - an effort that I and many of my colleagues consider quite important. What are the current plans for implementing this study, and what progress has been made?

Dr. Alexander: Considerable progress has been made in planning The National Children's Study. Currently 10 pilot studies are under way to address sampling and measurement questions with results anticipated later in this fiscal year. Notably, the National Children's Study Advisory Committee has been established under the Federal Advisory Committee Act with 21 Working Groups of Federal and non-Federal scientific experts all bringing a high level of scientific expertise to this extensive project. With the help of the expert Working Groups, the Advisory Committee will recommend the key hypotheses and additional pilot studies that are critical for designing and implementing the study. As of this response, the Advisory Committee has received proposals for 29 potential core hypotheses and 12 possible pilot studies. The Working Groups are carefully investigating and considering many more hypotheses and pilot studies. In an extensive multi-agency collaboration, staff of nine cabinet-level departments and independent agencies including a total of 30 distinct Federal entities have met and expressed strong interest in the study and reviewed ways they can participate in the study.

Current plans for the study are to carry out pilot studies through FY 2003 and into FY 2004, to finalize the core protocol by late FY 2003, and to pilot test the core protocol in FY 2004. It is expected that the initial study centers will be established in FY 2004 and that enrollment will start in mid FY 2005 and will continue through FY 2008.

TYPE II DIABETES IN CHILDREN

Mr. Obey: What research is underway at NIH involving the problem of type II diabetes in children? What can be done about this growing problem - not only in terms of new treatments but also in terms of public health interventions to reduce the incidence of this disease and prevent complications from arising?

Dr. Alexander: The NICHD is aware of the emerging epidemic of obesity-related Type 2 diabetes in children, especially in African-American and Latino populations. We are committed to supporting investigation in this area. The NICHD issued a request for applications with NIDDK to stimulate research on type 2 diabetes in the pediatric population. The applications supported through this initiative include research on type 2 diabetes in Hispanic adolescents, prevention of type 2 diabetes in high-risk teens, the prevalence and progression of the risk of type 2 diabetes in Mexican American youth, landmarks and the pathophysiology of type 2 diabetes in children and adolescents, screening for type 2 diabetes genes, and a school-based diabetes prevention program. A more recent RFA was designed to focus on research that would determine the mechanisms by which intrauterine environment and fetal metabolism predisposes individuals to chronic disease later in life and to determine whether these mechanisms may contribute to disparities in the prevalence of obesity and diabetes. This resulted in four recently funded R01 initiatives entitled *Genetics of Birth Weight in Mexican Americans*, *In Utero Metabolic Programming of the Offspring*, and *Programming Glucocorticoid Secretion During Fetal Life*. These grants examine the precursors to type 2 diabetes and aim to elucidate why low birthweight, in combination with adult obesity, is associated with a marked increase in the prevalence of insulin resistance syndrome.

Additionally, the NICHD funds research exploring the pathophysiology and treatment of Polycystic ovary syndrome (PCOS). This is a disorder affecting about 5 percent of reproductive-age women characterized by anovulation and excess production of androgens by the ovary. PCOS is frequently associated with insulin resistance and type 2 diabetes.

In addition to the research supported by the NICHD, the NIDDK has several initiatives under way to prevent and treat type 2 diabetes in children and also to prevent obesity–a major risk factor for the development of type 2 diabetes. Once researchers find interventions that are effective in preventing type 2 diabetes in children, NIDDK will use the National Diabetes Education Program (NDEP) to disseminate information to those who can benefit. The NDEP's "Diabetes in Children and Adolescent Work

Group" has been established to raise awareness among health care providers about diabetes in children and adolescents and to improve early diagnosis, treatment, and management of children with diabetes, as well as those at risk for diabetes. The Work Group has developed several resources for children with diabetes (www.ndep.nih.gov) including a fact sheet, resource directory, and annotated bibliography. A manual targeted to school personnel, which is designed to encourage optimal management of children with diabetes in the school setting, is under development. The Work Group is continuing its efforts to promote knowledge of the link between diabetes and obesity among children and adolescents. The Weight-control Information Network, a health information program of the NIDDK, is also developing science-based information about the overall health benefits of regular exercise and healthy eating for health care providers and the public, including parents with children who are overweight and at risk for developing type 2 diabetes.

The problem of the increased prevalence of obesity is a systemic one in our society, with several contributing factors, such as hours spent in front of the television set and personal computer screens; elimination of mandatory physical education in schools in every state; being bussed or driven to school; and, being kept indoors after school for safety reasons in households of working parents. All of the sedentary activity noted above facilitates storage of calories as fat, instead of expending calories during physical activity. The NICHD funded a project called Planet Health in ten school systems in Massachusetts. This project demonstrated that the prevalence of obesity in sixth and seventh grade girls was proportional to the number of hours they spent watching television. The good news is that the girls who were exposed to an intervention curriculum that taught them about the danger of sedentary behavior actually decreased the number of hours spent watching television and reversed their prevalence of obesity. Such curricula should be instituted widely in elementary and middle schools. Physical education should be considered just as important as scholastic education and should be widely reinstated in public schools throughout this country. School boards should rethink the issue of bussing children to school who live less than one-half mile from school. The more children walk to school, the more calories they will burn, and the fewer they will store as fat tissue. Children need to be encouraged to incorporate more activity into their daily lives, such as bicycling, skate-boarding, dancing, playing sports, etc. However, the physical environment will have to be altered to encourage such activities safely. More bike paths and safe play areas should be built in every community across the nation in order to facilitate such a profound behavioral change.

There is no question that children today are more sedentary than they were 25 years ago. Whether or not their caloric intake has increased significantly over the same period of time is unclear, owing to a lack of reliable historical data on caloric intake in a population-based sample of children, and owing to the use of different kinds of food intake inventories over the years. However, there is no question that the consumption of soft drinks has increased greatly over the past quarter-century, and now many school systems are signing 'pouring contracts' with soft drink companies that entail the installation of soft-drink vending machines in the schools. Many of our nation's

children eat three or four meals per week in fast-food restaurants. These restaurants typically feature super-sized servings of fried and fat-laden food as well as 'thirst-busting'-sized soft drinks. Our nation's children are certainly being exposed to a greater intake of calories now than they were 25 years ago. This trend will be difficult to reverse, in view of children's predilection for fatty and fried foods and for super-sized servings, as shown in focus groups of children. Perhaps working with fast-food companies to decrease serving sizes and to offer more heart-healthy menus would ameliorate the trend to ever-greater caloric density of fast-food menus and serving sizes.

MUSCULOSKELETAL MEDICINE

Mr. Obey: Your written statement mentions that NIAMS is working to develop a trans-NIH collaboration in musculoskeletal medicine. Please tell us more about what you are hoping to accomplish and the progress that has been made so far.

Dr. Katz: The NIAMS joined with six other NIH components to focus resources to enhance and expand NIH collaborations in musculoskeletal medicine. This effort includes the creation of a new entity for bone and cartilage biology research, which will be located across from the NIH campus at the National Naval Medical Center in a renovated set of buildings that offer significant research space, as well as access to new clinical space. This trans-NIH collaborative activity will build on the strengths that are already present and are beginning to be coordinated, enhance research productivity through synergy of the programs, develop new programs, recruit new investigators, and coordinate with existing and newly developed clinical programs.

We envision this new entity as encompassing state-of-the-art and innovative fundamental science, clinical studies, and translational research. It will provide a focus for a wide array of basic and clinical research on bone and cartilage medicine, development, genetics, and musculoskeletal disease. In addition, this collaborative effort will explore and advance the application of the emerging discipline of tissue engineering for reconstituting damaged skeletal components; serve as a scientific resource for a broad spectrum of investigators on the NIH campus, around the country, and around the world; and provide leadership in both research training and education in the full array of basic, clinical, and translational research related to the musculoskeletal system.

AUTOIMMUNE DISEASES

Mr. Obey: I know that many of the diseases addressed by your Institute are autoimmune in nature, and disproportionately affect women. What is NIAMS doing to help develop therapies for these diseases?

Dr. Katz: Research has resulted in significant progress in our understanding of autoimmune diseases, but it remains a puzzle why, in some patients, the body's own cells turn against the body's own tissues. A number of arthritic and skin diseases in the

research mandate of the NIAMS have their origin in autoimmunity, and research on this is integral to the Institute. Diseases in this category include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren's syndrome, alopecia areata, scleroderma, and many blistering skin diseases. Many of these chronic conditions affect women much more often than men, and all have a significant impact on the quality of life and productivity of affected patients and their families. Because many Institutes and Centers at the NIH have a strong interest and investment in autoimmunity, the agency established an Autoimmune Diseases Coordinating Committee to stimulate additional research in this area and enhance collaborative approaches. The NIAMS is a very active member of this committee.

The NIAMS supports a broad range of research on autoimmune diseases, including studies aimed at developing new treatments for these conditions. Such projects include work to test innovative therapies for RA, scleroderma, SLE and ankylosing spondylitis. The Institute is also supporting clinical trials to study immune-modulating therapies for RA and psoriasis. Earlier this year, the Institute sponsored a major scientific meeting on targets for new therapeutics for SLE – recommendations from this meeting will be considered as the Institute develops future initiatives in this area. In addition, the NIAMS recently established an Autoimmunity Branch within the Institute's intramural research program to explore the cellular and molecular basis of autoimmunity. Insights from this laboratory research will help inform approaches to new therapeutics. Finally, the Institute is committed to developing and disseminating science-based health education materials for patients and families affected by autoimmune diseases. To this end, the NIAMS recently published a "Questions and Answers" booklet on autoimmunity. The booklet includes information about diagnosis and treatment of these conditions, and underscores the importance of future research to enhance our understanding of autoimmunity.

AUTOIMMUNE DISEASE RESEARCH

Ms. Pelosi: Dr. Katz, I am pleased to learn of the increased attention NIH is placing in the area of autoimmune disease research, particularly scleroderma. Just in the past couple of months NIAMS announced 10 new research grants funded for scleroderma research. NIAMS is to be commended for the additional commitment it has placed in this area. As with other autoimmune disease research, I remained concerned with the lack of new researchers entering the field. I know that your department shares this concern and hope that we can work together to devise a plan to help address the problem. I would welcome any comments you may have on this issue.

Dr. Katz: The challenge of attracting new investigators to biomedical research is not unique to the field of autoimmune diseases. Indeed, the NIAMS, along with many other Institutes and Centers at the NIH, has worked hard to develop mechanisms of support that promote the careers of new and mid-level scientists. These efforts include a small grants program for new investigators; educational loan repayment for scientists who are committed to clinical, pediatric, and minority health research; career development awards in mentored, patient-oriented research; and supplements to promote the reentry of scientists to biomedical and behavioral research following time off to care for children or attend to other family responsibilities, in conjunction with the NIH Office of Research on Women's Health. We hope that these targeted efforts, in addition to our broad support for research and training across the spectrum of rheumatic, musculoskeletal, and skin diseases, will ensure a steady pipeline of investigators for all of the diseases that we study, including autoimmune disorders.

NATIONAL CHILDREN'S COHORT STUDY

Ms. Pelosi: Children are more vulnerable than adults to the adverse health outcomes that may result from exposure to environmental contaminants because their bodies are still developing.

As you know, the Child Health Act authorized a National Longitudinal Children's Cohort Study that will be used to investigate basic mechanisms of developmental disorders and environmental processes and incorporate a range of factors to enable a complete assessment of the physical, chemical, biological, and psychological environmental influences on children's well being.

I have said many times that children must be our nation's top priority - their health, their education, and their futures. The information derived from this study will be an extremely valuable resource as we strive to develop policies that improve the lives of children.

In each of the past two years, report language ' has emphasized the high priority that the Subcommittee places on this study, and NICHD has been asked to allocate sufficient funds to have the study up and running by the end of 2003. Given the significant funding increases that NICHD has received over the past two years, we should be on track to meet that timetable. Are we?

Dr. Alexander: The NCS timetable is to begin enrollment into the full study at the end of FY 2004. This allowed for the establishment of the chartered National Children's Study Advisory Committee to be able to obtain input from experts in academia, industry, and other non-governmental organizations and for the necessary pilot studies to develop the appropriate measurements and the study design. Current plans for the study are to carry out pilot studies through FY 2003 and into FY 2004, to finalize the core protocol by late FY 2003, and to pilot test the core protocol in FY 2004. It is expected that the initial study centers will be established in FY 2004 and that enrollment will start in mid FY 2005 and continue through FY 2008.

Ms. Pelosi: How many FTE's are devoted specifically to managing this enormous enterprise?

Dr. Alexander: NICHD has devoted one scientist, one planning and coordination analyst, and two administrative support positions to the planning effort of this study. The other lead agencies, NIEHS, CDC, and EPA, have asked their representatives to the Inter-agency Coordinating Committee to devote a combined total of three FTE's that involve nine scientists to this effort.

Ms. Pelosi: How much is NICHD planning to allocate in FY03?

Dr. Alexander: In FY 2003 NICHD is planning to allocate $6.5 million to the NCS. FY 2003 is the third year of a four-year planning effort.

EARLY DETECTION OF BREAST CANCER

Mrs. Lowey: As you know, I am very concerned about the recent controversy surrounding mammography. I believe that the debate over the data on the effectiveness of mammography only underscores the need for a better, more effective and less invasive method for the early detection of breast cancer. Could you tell me what activities are ongoing both across institutes as well as with outside researchers to develop the next step in the early detection of breast cancer? How can we increase our efforts?

Dr. von Eschenbach: The NCI is taking a very active role in both improving on currently available technology as well as developing new methods for the early detection of breast cancer.

Digital mammography is similar in many ways to conventional (film-screen) mammography except that the image is captured on an electronic receptor (also called a detector) instead of on film. The electronic receptors capture more information than film. The electronic image can be processed in a variety of ways by computer software, and pilot data suggest that this computerized image processing will result in detection of more cancers and elimination of more false positives than in conventional mammography. Furthermore, software can be used to automatically detect suspicious areas on the mammogram and call these to the attention of the radiologist. This should result in more consistent interpretation of mammograms and fewer missed cancers.

Different manufacturers use different technologies for their electronic detectors, and it is not yet clear whether they are all equal to each other and better than conventional mammography. Two technologies have been approved by the FDA, and two others are available in test units at several sites in the United States. NCI is funding a large trial comparing digital mammography with conventional mammography. Technologies from four different manufacturers are included. The trial will accrue approximately 49,000 women at 19 sites in the United States over 2 years. Results should be available in approximately 3 years.

There are several imaging technologies that are being studied or proposed as alternatives or adjuncts to mammography for early detection of breast cancer. Two imaging technologies that are relatively mature and have been suggested for early breast cancer detection are ultrasound and Magnetic Resonance Imaging (MRI). NCI is funding a cooperative group of fourteen institutions doing a pilot study of MRI for early breast cancer screening in women at high risk. That pilot study is almost complete and results are expected within a year or two. Pilot studies of ultrasound for breast cancer detection have been completed and show some promising results, although somewhat dependent on the experience of the people doing the ultrasound. NCI funds a cooperative group for multicenter imaging clinical trials called the American College of Radiology Imaging Network (ACRIN). Within ACRIN there is now a protocol development team putting together a proposal for a large multicenter trial of ultrasound for early breast cancer detection.

Computed tomography (CT) provides 3-dimensional images of body structure. Recent advances in CT technology make it possible to acquire CT images in seconds, and use much lower doses of radiation than previously. The potential advantage of using CT for breast imaging is that it could be done without applying compression to the breast. NCI is funding a Bioengineering Research Partnership (BRP) grant for development of a dedicated breast CT scanner that could produce 3-D images of the breast using no more radiation than is used in conventional mammography. Such a device could potentially be used for screening, and might find increased acceptance among women compared to mammography because of the absence of the need for compression.

There are several less mature imaging technologies that have been proposed or are being investigated for early breast cancer detection. Thermography is a technique that detects changes in skin temperature caused by changes in blood flow. Thermography was tested for early breast cancer detection in the 1970's but abandoned because of poor sensitivity. In recent years the FDA approved two new devices for thermography. However thermography is still not widely accepted for screening because of high false positive rates and low sensitivity. NCI is funding some investigator-initiated research projects that seek to improved thermography for breast cancer detection.

Electrical impedance devices work by passing a small electric current through the breast and measuring the voltage changes on the surface of the skin. An FDA approved device is commercially available, but is not widely used for screening because of relatively poor sensitivity and high false positive rates. For comparison, the sensitivity and specificity of ultrasound and MRI have both been better in pilot trials than the corresponding values for thermography or electrical impedance.

Nuclear medicine techniques are used to help to distinguish benign from malignant breast masses, but so far have not been shown to be practical for wide spread screening. Scintimammography using a radiolabeled compound called sestamibi is useful in evaluating masses detected by mammography or by physical examination, but it is not considered useful for screening because it does not reliably detect cancer smaller than one centimeter. Similarly, PET scanning with a radiolabeled glucose compound is useful for evaluating breast abnormalities, but is not considered useful for screening because it does not reliably detect cancer smaller than one centimeter, and it is relatively expensive. NCI is funding some investigator-initiated research projects that aim to develop dedicated PET scanners for the breast that would make the examination considerably cheaper and would have improved resolution for finding small cancers. If these goals are achieved, then PET scanning might be a reliable screening modality.

There are a variety of optical technologies that use light from lasers in the visible spectrum or in the near-infrared spectrum. These can detect differences between oxygenated and non-oxygenated hemoglobin, or can detect signals from optical contrast agents that have been injected. These technologies are in an early stage of development

and so it is difficult at this time to predict whether they will be feasible for screening. However some early results look very promising and optical technologies have the advantages of being relatively inexpensive and not using ionizing radiation. NCI funds several research projects looking at a variety of different optical technologies, and will soon issue a Request for Applications for a network for optical technologies development.

There are a variety of other imaging modalities which are in very early stages of development for possible detection of early breast cancer. These include technologies such as magnetic resonance spectroscopy, magnetomammography, Hall effect imaging (passing an electric pulse through tissue while exposed to a magnetic field), thermo-acoustic computed tomography, and focused microwaves for imaging. Again, NCI funds a wide variety of research projects on these imaging technologies, including a program project entitled, "Alternative Breast Cancer Imaging Modalities." It is too early to predict whether any of these will actually become useful for early breast cancer detection.

Many imaging modalities rely on the presence or absence of structural change for detecting abnormality. One of the uncertainties about a structural change is whether it represents a biologically aggressive or non-aggressive cancer. Better understanding of the biology of breast cancer is needed. As our knowledge about the biology of breast cancer improves, some of the novel imaging techniques described above that can detect functional changes may become more feasible and indicate lesions that definitely need to be removed. In the near term, it is likely that MRI and ultrasound will be found to be useful for screening certain populations of women for whom mammography is inadequate, such as young women at high risk and women with very dense breast tissue.

In addition to imaging technology, NCI is investing in new biologic tests to improve our ability to identify cancer cells in their earliest possible stages of development. Among the research being supported:

- Molecular Analysis - NCI's Innovative Molecular Analysis Technologies Program (IMAT) supports the development of non-invasive techniques for identifying molecular changes that distinguish cancer cells from normal cells. More than 100 research projects are under way, focusing on new approaches to analyze DNA, RNA, and proteins.

- Proteomics: Finding Protein Patterns - Proteomics is the systematic study of protein expression and function. In the Clinical Proteomics Program, a joint initiative of NCI and FDA, researchers are discovering differences in patterns of protein in the blood from cancer patients compared to people without cancer and applying this knowledge to early detection of breast cancer.

- Biomarkers - NCI's Early Detection Research Network (EDRN) is the first comprehensive network to develop and validate early detection markers for cancer. Researchers are studying a variety of molecules, proteins, genes, and other biological substances that may be the earliest warning signs that normal cells are on the road to becoming cancerous. Their discoveries are then translated into methods for detecting warning signals, sometimes even before full-blown cancer can develop.

- Finding Fingerprints of Cancer Cells: The Molecular Classification of Tumors - All cells have unique "signatures" - special characteristics related to which genes are active and which proteins or other products the cell manufactures. During the transformation of a normal cell to a cancer cell, the cell's signature changes, and the change becomes a signal of the presence of cancer. Researchers are developing profiles of molecular alterations in human tumors, such as breast cancer, using DNA, RNA, or protein-based technologies. This technology holds promise for improving the early detection, diagnosis, and treatment of cancer.

Over the years, researchers have focused on examination of cells shed by breast tissue into the ducts. Investigators have now developed techniques for collecting nipple aspirates and ductal lavage and hope that it may be possible to evaluate suspicious breast masses detected by mammography by analyzing these secretions. It may be possible to spare at least some women the need to undergo a surgical biopsy.

As we endeavor to make new screening technologies available to women, it is important to understand how breast cancer screening is being used in the community. NCI has established the Breast Cancer Surveillance Consortium (BCSC), a cooperative agreement between the NCI and investigators at medical research centers across the country. This project was designed to evaluate the performance of screening mammography in community practice in the United States by linking data from mammography registries with data on cancer outcomes from pathology laboratories or cancer registries. The Consortium's database contains information on over 2.2 million screening mammographic examinations and 28,000 breast cancer cases. Anticipating the need to track the diffusion of new screening technologies in clinical practice, the Consortium is now developing measures for tracking the use of digital mammography and will serve as a model for evaluating the use of other new technologies as they emerge.

There is no doubt that thousands of women are alive today because their breast cancers were treated successfully after having been detected by mammography. There also is no doubt that we have plenty of opportunity for improvement. The examples of our work that I have described here demonstrate our commitment to realizing this improvement. We have designated cancer imaging and defining the molecular signatures of cancer cells among our highest scientific priorities, as outlined in our budget request document, *The Nation's Investment in Cancer Research for Fiscal Year 2003*. NCI will continue to strive to ensure that our research findings are translated quickly into effective interventions that lead to longer and better lives for breast cancer patients.

The NCI has agreed to be a sponsor for a new study by the Institute of Medicine (IOM) that is specifically aimed at addressing the time required for new innovations in breast cancer detection to reach the public. The study will build on the groundwork laid by the 2001 IOM report, *Mammography and Beyond: Developing Technologies for the Early Detection of Breast Cancer*. The study will be led by the IOM National Cancer Policy Board in collaboration with the Board on Science, Technology, and Economic Policy of the National Research Council. The study will consider which of the new and existing approaches might hold the greatest promise for improving the early detection and diagnosis of breast cancer. In addition, the study will analyze the degree to which different factors present opportunities or barriers to the development and diffusion of medical innovations, in general; and, in particular, those opportunities or barriers related to innovative approaches to the detection of breast cancer. Possible strategies to enhance the opportunities and to lower barriers will be evaluated.

The study will be conducted in two phases. During the first phase, a group of leaders with diverse backgrounds will be appointed to formulate the study plan, and to determine if the study charge needs to be refined. The second phase would be conducting the 15-month study described in the proposal. The committee will organize two roundtable workshops at which they will hear from experts in oncology and cancer biology, clinical management of breast cancer, breast cancer detection, different imaging techniques, bioengineering, the economics of health and technological innovation, and regulation of medical devices. As background for the workshops, the committee will commission approximately 6 background papers. Following the workshops, the committee will hold two meetings to revise their draft report. The project will seek the input from the following sectors:

- the biotechnology, pharmaceutical, and imaging device industries;
- private foundations involved in supporting research, development, and diffusion of medical innovations relevant to breast cancer detection and diagnosis; and
- federal agencies, including CMS, National Institute of Science and Technology (NIST), National Aeronautical and Space Agency (NASA), and the Department of Defense (DOD), and the NIH particularly the National Cancer Institute (NCI), the NCI-Industry Forum, and the National Institute of Biomedical Imaging and Bioengineering (NIBIB).

Finally, the study will consider how to broaden public perspectives in terms of how information about new approaches can be most effectively communicated. The committee will produce a report that will be disseminated to stakeholders, policymakers, and policy implementers. Those groups include:

- Federal agencies
- Members of Congress and their staff

- cancer patient and advocacy organizations
- women's health organizations
- research community, including professional societies involved in cancer research
- groups involved in medical technology development (including diagnostics and therapeutic treatments)

PEDIATRIC ENDOCRINOLOGISTS

Mrs. Lowey: Dr. Alexander, in the FY 2002 bill, the committee expressed concern about a shortage of pediatric endocrinologists, and urged NICHD to enhance efforts to remedy the shortage. What steps has NICHD taken to solve this shortage?

Dr. Alexander: This year, the NICHD established a postdoctoral training program for pediatricians during or just after their subspecialty training. Six pediatric departments will be funded in July, 2002. These institutional grants will provide funds to nascent pediatric endocrinologists and other subspecialties at the discretion of the institution. Furthermore, we will soon issue a second RFA that explicitly states our interest in programs focusing exclusively on pediatric endocrinology training.

The NICHD Division of Intramural Research currently has a nationally-recognized training program in pediatric endocrinology. This program collaborates with Georgetown University Medical Center. Additionally, the pediatric endocrinology program serves as a training site for the Uniformed Services University of the Health Sciences (USUHS) pediatric endocrine fellows, as well as providing clinical and research exposure for clinical fellows in adult endocrinology for both the NICHD and the NIDDK.

PEDIATRIC TESTING

Ms. DeLauro: In November of last year Congress passed H.R. 2887, the Best Pharmaceuticals for Children Act. The law reauthorized section 505A of the Food Drug and Cosmetic Act, commonly known as the pediatric exclusivity provision. In addition to giving manufacturers an economic incentive to conduct pediatric clinical trials, the bill authorized $200 million for the NIH to award contracts to organizations that would conduct pediatric studies on drugs that have no patent term or marketing exclusivity remaining. This provision was included in the bill to fill gaps in the original pediatric exclusivity provision. Does your current budget include the $200 million fund authorized by the legislation and is it included in your budget request for FY 2003? If so, where is it in the NIH budget and when will the program begin? If it is not in the budget request, why is it not included? How will NIH create this program without funding?

Dr. Alexander: The Best Pharmaceuticals Act for Children was not signed into law until January 4, 2002, after Congressional action on the FY 2002 appropriation had been completed. However, NIH is fully committed to implementing the goals of this Act, and has already begun to do so. Several of the provisions on the Best Pharmaceuticals for Children Act require consultation with the Food and Drug Administration (FDA) to implement them. NIH and FDA have held initial meetings to begin determining the list of priority drugs for pediatric testing, which is due to Congress by January 2003. From that list, NIH and FDA must determine appropriate off-patient candidates, and FDA must first request the holders of the patents to conduct the studies necessary to establish labeling for pediatric uses. NIH would then be in position to determine and solicit proposals for any remaining contracted studies. To get this process started, NIH has decided to dedicate about $7 million in FY 2002 funds to ready the existing infrastructure to conduct clinical trials on those drugs, once determined, primarily through the National Institute of Child Health and Human Development's Pediatric Pharmacology Research Units (PPRUs). Because the PPRU Network already exists, some testing can be conducted once the priority list of drugs has been determined. For FY 2003, NIH will make $25 million available to fund research contracts on pediatric drug use under the new authority.

Ms. DeLauro: How do you work with FDA to enforce this provision of the law?

Dr. Alexander: Several provisions of The Best Pharmaceuticals for Children Act direct the NIH and the FDA to consult with each other in carrying out the new law. The two agencies, which have worked together for many years in implementing the Better Pharmaceuticals for Children Act, have already begun to meet regarding the development of the priority list of drugs for pediatric testing, and will continue to work together on the other relevant provisions of the bill.

SCLERODERMA

Ms. DeLauro: Dr. Katz, I am pleased to learn that NIAMS recently funded a study to be conducted at the University of Connecticut School of Medicine and Dentistry regarding scleroderma. This joint effort by NIAMS and NIH's Office of Women's Health may shed light on the causes of this terrible disease and I am delighted that researchers in my home state will participate. I am concerned however, that not enough resources are being allocated to such research and as a result not enough researchers are drawn into the study of such rare autoimmune diseases. It is critically important that the department continue to find ways to spawn interest in areas of autoimmune diseases as it has in other areas of research. Could you please update me on the efforts currently underway at NIAMS in regards to scleroderma?

Dr. Katz: Currently, there is no treatment that controls or stops the underlying problem that patients with scleroderma face: namely, the overproduction of collagen, a key component of the body's connective tissue. Little is known about the cellular changes that cause the skin and organs to harden, and the disease is often difficult to diagnose. Understanding the early cellular and molecular changes in scleroderma will help scientists to develop better therapies. The new projects awarded by the NIAMS, in partnership with the NIH Office of Research on Women's Health, will increase our understanding of the causes of scleroderma, and bring us closer to finding effective treatments. These new studies, which were initiated in follow-up to a major scientific conference and special research solicitation issued by the NIAMS, include investigations in three key areas: cellular and molecular processes in the disease; cell transfer between mother and child in scleroderma; and innovative therapies.

To facilitate translational research in this area, the NIAMS supports two Specialized Centers of Research in scleroderma, one of which is conducting investigations of the biological processes that cause the progression of the disease--gaining a better understanding of these processes could lead to new treatment approaches. The Institute also recently funded a multidisciplinary clinical research center on pediatric rheumatic diseases, such as juvenile scleroderma. In addition, the Institute is supporting the development of a national scleroderma family registry and DNA repository, with the overall objective of identifying genes that influence susceptibility to the disease. The NIAMS also funds a number of projects on autoimmunity and autoimmune diseases such as scleroderma, and has recently published health booklets on scleroderma and autoimmunity intended for the public, affected patients, and their families.

DISPARITIES RESEARCH PORTFOLIO

Mr. Jackson: Dr. Ruffin, one of the goals of the legislation that established the National Center on Minority Health and Health Disparities was to provide the Center with the authority to directly award peer-reviewed research grants. Can you update the subcommittee on the Center's health status disparities research portfolio? Also, can you update us on your research collaborations with other NIH institutes and centers?

Dr. Ruffin: The Center currently is developing its research priorities and will consult with the NCMHD Advisory Council regarding these activities. The NCMHD expects to publish its first research program announcements early in fiscal year 2003. We also will be funding research as part of our Project EXPORT Centers of Excellence Program starting in September.

DISPARITIES

Mr. Jackson: Dr. Ruffin, I understand that the National Center made its first round of Research Endowment awards to five historically black health professions schools last year. Do you anticipate making any additional awards as part of this initial round?

Dr. Ruffin: The NCMHD piloted the Research Endowment Program in FY 2001. NCMHD was able to make five awards totaling $21 million in September, 2001. The additional two awards will be made with FY 2002 funds.

RESEARCH ENDOWMENT AND CENTERS OF EXCELLENCE

Mr. Jackson: Moreover, can you update the subcommittee on your plans for the Research Endowment and Centers of Excellence programs in FY03?

Dr. Ruffin: NCMHD plans to issue another competition of the Research Endowment Program in FY 2003. The projected budget for this program is $31 million. NCMHD will monitor these endowments throughout the life of the award.

In FY 2003, NCMHD will also issue another competition of the Centers of Excellence program. $28.5 million is included in the Center's FY 2003 budget for this initiative.

GLOMULAR INJURY

Mr. Jackson: Dr. Ruffin, in its FY02 report the subcommittee encouraged the National Center to work with the National Institute of Diabetes and Digestive and Kidney Diseases on research related to glomerular injury. Can you update the subcommittee on the status of this collaboration?

Dr. Ruffin: The NCMHD currently partners with the NIDDK to support and conduct a number of projects aimed at understanding as well as protecting against glomerular injury. Glomerular injury, a group of diseases that affect the filtering mechanisms of the kidney, are more prevalent among African-Americans than the general population. The projects include the genetic analysis of kidney disease, blood pressure reduction and protection of glomerular tissue by drugs like captopril, and improving glucose control, a major cause of glomerular injury in diabetes. The NCMHD expects to continue to partner with the NIDDK to increase knowledge on the causes of glomerular injury as well as improve the diagnosis of and develop new therapies for reducing and protecting against glomerular injury.

NCMHD FUNDING

Mr. Jackson: What areas of health disparities research does the NCMHD intend to rely on other ICs to fund? Does the NCMHD have specific joint funding agreements with any IC?

Dr. Ruffin: The NCMHD recognizes that the goal of reducing and ultimately eliminating health disparities cannot be accomplished by the Center alone, but rather requires an interdisciplinary approach involving a host of organizations within NIH and across the nation. The other NIH Institutes and Centers (ICs) will focus their efforts in health disparities within research areas under the purview of their specific missions. Their activities may involve collaboration with the NCMHD, other ICs, and/or their other research partners across the country. As the coordinator of NIH health disparities research activities, the NCMHD will leverage IC resources by continuing to co-fund a vast array of research projects with the ICs, while at the same time reviewing the full spectrum of research activities and identifying gaps and opportunities for additional research to be funded either by the Center or by the Center in collaboration with others.

The Center collaborates on a multitude of research projects with the other NIH Institutes and Centers (ICs). During fiscal year 2001, the NCMHD provided $100 million of its funding for projects it co-funded with the other NIH ICs. The Center currently is co-funding with the other ICs research projects in a multitude of areas, such as cancer, heart disease, diabetes, HIV/AIDS, infant mortality, oral health, and mental health.

NIH IC FUNDING OF HEALTH DISPARITIES RESEARCH

Mr. Jackson: How is the Center tracking other IC's funding of health disparities research?

Dr. Ruffin: The NCMHD has addressed its coordination and tracking responsibilities in a number of ways. The Center has developed the first draft NIH Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities, which contains submissions from each NIH Institute and Center (IC)

describing its planned activities in health disparities in the areas of research, research infrastructure, and outreach. The Plan is now under review within the NIH Office of the Director. Working with the ICs, the Center will identify additional opportunities for collaboration across ICs and identify research gaps and new research opportunities. Additionally, the Center will report on the progress of all ICs in the Annual Report of NIH health disparities activities. The NCMHD plans to develop a database of information regarding these NIH activities that will aide in tracking, monitoring, and reporting on their status. To provide further coordination across the NIH, the Center will utilize a trans-NIH coordinating committee to guide our efforts.

RESEARCH INFRASTRUCTURE

Mr. Jackson: What are NCMHD's research infrastructure objectives?

Dr. Ruffin: Building capacity for minority health and other health disparities research is a high priority for the NCMHD. Accordingly, the Center will focus its efforts in two areas: supporting research training and career development and providing support for institutional resources.

Mr. Jackson: What is your approach for increasing the research infrastructure in minority serving institutions and in medically underserved areas?

Dr. Ruffin: Building capacity for minority health and other health disparities research is a high priority for the NCMHD. A major approach of the Center is to develop a cadre of researchers with expertise in minority health and other health disparities research. To accomplish this, the Center has established its extramural loan repayment programs. Another approach for the NCMHD is to promote and support research capacity building activities in racial and ethnic minority and medically underserved communities. To accomplish this, the Center is implementing its Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training Program (Project EXPORT). These centers will promote the conduct of minority health and/or health disparities research aimed at reducing disparities in health; promote the participation of members of health disparity groups in biomedical and behavioral research and prevention and intervention activities through education and training; and build research capacity in minority serving institutions. The NCMHD also will accomplish this approach through the Endowment Program for Section 736 [Public Health Service Act] Institutions with currently funded Programs of Excellence in Health Professions Education for Underrepresented Minority Individuals. This program will build research and training capacity in institutions that make significant investments in the education and training of underrepresented minority and socio-economically disadvantaged individuals. An additional NCMHD approach is to develop and refine research tools, survey instruments, and databases that are culturally sensitive, culturally competent and specifically designed for minority and other health disparities populations. In this regard, the Center plans to implement a knowledge repository database to facilitate the retrieval, analysis and dissemination of minority health and other health disparity research, infrastructure and outreach.

RESEARCH ENDOWMENTS

Mr. Jackson: What is the status of the Research Endowment Program?

Dr. Ruffin: The NCMHD plans another round of awards in FY 2002 and, this spring, will issue an RFA announcing this year's competition. We have budgeted $31 million for the Research Endowment Program in FY 2002. NCMHD will monitor the endowment awards throughout the life of the award.

PROJECT EXPORT COE

Mr. Jackson: What is the status of the Centers of Excellence for Research Education and Training Program?

Dr. Ruffin: The NCMHD issued three RFAs (totaling $17.5 million) for the Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project EXPORT) in February 2002. Each RFA is for a different funding mechanism focused on institutions with differing levels of research infrastructure: Developmental Grant Awards (R24), Exploratory Grant Awards (P20), and Center Awards (P60). To assist the stakeholder community with its application efforts, the NCMHD conducted four technical assistance workshops in February and March, 2002. Approximately 325 researchers and business officials from educational institutions that are involved in health disparity research attended the workshops. Feedback has been overwhelmingly positive, and the workshops have generated heightened interest in the RFAs. Applications are due in May, 2002 with funding scheduled for September 2002.

LOAN REPAYMENT PROGRAM

Mr. Jackson: What is the status of the Loan Repayment Program, and how many awards were made this past year?

Dr. Ruffin: The Loan Repayment Program for Health Disparities Research (HDR-LRP) was established in FY 2001. It commenced on July 30, 2002. The NCMHD received 78 applications and made 28 awards totaling $1.828 million. Seventeen of the 28 awards were made to individuals that belonged to health disparity populations. The average dollar assistance of awards made for FY01 is estimated at $65,309 (This figure includes loan repayment and tax reimbursement for the initial two-year contract).

Examples of the types of research the participants are conducting include, but are not limited to, the following: Racial/ethnic differences in the use of hospice amongst cancer patients; Socioeconomic and racial/ethic disparities in maternal and infant health; Breast cancer risk reduction in African-American women; Quality of mental healthcare

for American Indian adolescents; Tobacco use, prevention and cessation amongst Native Americans; Relationship between acculturation and healthcare views; and Disproportionate impact of Hepatitis C Virus (HCV) on minority populations.

For FY 2002, the NCMHD is currently seeking approval of its notice announcing the HDR-LRP and anticipates beginning the application process in May with awards being made by September, 2002.

COMPLIANCE WITH PUBLIC LAW

Mr. Jackson: How has the NCMHD addressed its mandate to coordinate minority health and health disparities research?

Dr. Ruffin: The NCMHD has addressed its coordination responsibilities in a number of ways. The Center has developed the first draft NIH Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities, which contains submissions from each NIH Institute and Center (IC) describing its planned activities in health disparities in the areas of research, research infrastructure, and outreach. The Plan is now under review within the NIH Office of the Director. Working with the ICs, the Center will identify additional opportunities for collaboration across ICs and identify research gaps and new research opportunities. Additionally, the Center will report on the progress of all ICs in the Annual Report of NIH health disparities activities. The NCMHD plans to develop the Health Disparities Information System, a database that will aide in tracking, monitoring, and reporting on the status of NIH supported minority health and health disparities initiatives. To provide further coordination across the NIH, the Center will utilize a trans-NIH coordinating committee to guide our efforts.

ADVISORY COUNCIL

Mr. Jackson: What is the status of your advisory council? How has it impacted the Center's ability to accomplish its goals?

Dr. Ruffin: The membership of the NCMHD Advisory Council has been approved by the Secretary, HHS. The Center hopes to convene two meetings of the Council in 2002, one in September and one at an earlier date to be confirmed.

With the establishment of the Advisory Council, the Center will be able to independently fund its own grant awards. Prior to this time, however, it was necessary for the Center to utilize an Advisory Council of another NIH IC for the second level review of such awards.

COLLABORATIONS

Mr. Jackson: What is the nature of the coordination between the NCMHD and the other NIH ICs?

Dr. Ruffin: The Center consults directly with the NIH Institutes and Centers (ICs) regarding health disparities research priorities and identifies areas of potential co-funding with each IC.

TUESDAY, APRIL 16, 2002.

DEPARTMENT OF HEALTH AND HUMAN SERVICES, NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. RUTH L. KIRSCHSTEIN, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. CLAUDE LENFANT, DIRECTOR, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
DR. FRANCIS COLLINS, DIRECTOR, NATIONAL HUMAN GENOME RESEARCH INSTITUTE
DR. KENNETH OLDEN, DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
DR. PAUL SIEVING, DIRECTOR, NATIONAL EYE INSTITUTE
DR. LAWRENCE TABAK, DIRECTOR, NATIONAL INSTITUTE FOR DENTAL AND CRANIOFACIAL RESEARCH
DR. PATRICIA GRADY, DIRECTOR, NATIONAL INSTITUTE OF NURSING RESEARCH
DR. DONALD LINDBERG, DIRECTOR, NATIONAL LIBRARY OF MEDICINE
DR. RAYNARD KINGTON, ACTING DIRECTOR, NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

CAREER OF CAROL MURPHY

Mr. REGULA. I would like to start the meeting of our subcommittee. We have a lot of important testimony today, but first of all, I want to say that this is Carol Murphy's last day. She is going to take over the clerkship of the D.C. committee, so she will have some new and interesting challenges, and I think perhaps her experience in dealing with health issues will be of constructive value to her in dealing with D.C. because they probably have some of the different form but nevertheless challenging issues and, Carol, we wish you well in your new role. You have been a wonderful staff person. You have been providing great leadership in dealing with the issues that confront this subcommittee. It is a very important subcommittee because the things we do touch the lives of all 280,000,000 Americans either in education or in health care or, in some cases, in labor issues.

Mr. Obey, would you like to make a few comments before we start the hearing?

Mr. OBEY. You bet. I simply would like to say, Carol, I think you are making a terrible mistake.

Mr. REGULA. That is encouraging.

Mr. OBEY. I really hate to see you leave. I mean I served my penance on the D.C. Subcommittee years ago. I think you are a perfect example of how this institution works because there are so many people at the staff level who do all of or almost all of the real work and who do most of the negotiating and who come up with the

ideas that enable the politicians in this place to occasionally reach common ground even when sometimes it is very hard to find, and in the process you have managed to help an awful lot of people who will never know your name or never even know you were here, and I think on behalf of them, we both owe you a profound vote of thanks.

Mr. REGULA. Mr. Obey, I think you said it well. The American people were fortunate that you gave the years of service to this committee that you have, and many of the products of this committee in legislative initiatives have resulted in Carol's work ambition. So we are pleased with her service and we all wish you well with the new challenge.

Dr. Kirschstein, we are glad to have you back and to have some members of your team here. We will wait for an opening statement from you. Put your full statement in the record, and then you can introduce the members of your team as they each make their presentation.

DR. KIRSCHSTEIN'S OPENING STATEMENT

Dr. KIRSCHSTEIN. Mr. Chairman, Mr. Obey, we too at NIH want to thank Carol Murphy for all that she has done. She has been extraordinarily helpful to us and we feel that we are going to miss you just about as much as they are going to miss you. We have the opportunity to see some of these gentlemen again next year, and we hope you will come and visit the committee so we can retain our friendship.

Mr. Chairman, we again want to tell you how pleased we are to have had these opportunities to present our programs. This is the last of the panel sessions for NIH. This is the continuum of presentations and we ended with a discussion of disease prevention and health promotion. In this area, as in all others, each of the institutes has a major role not only doing research but in communicating the results of research. In fact, communication is the critical link between the scientific knowledge we uncover and preventing disease, maintaining healthy lives and managing chronic diseases and conditions. These research and communications activities must be carefully coordinated among the NIH institutes and centers, among these institutes and centers and other agencies, such as CDC and the Food and Drug Administration, the Substance Abuse and Mental Health Services Administration, and among all the agencies of the Federal Government, NIH, DHHS, USDA, the National Science Foundation, et cetera.

I have submitted an opening statement which highlights a few of them which brings forward material that my colleagues will present which is representative of what all the institutes and centers do. The panel members with me today are, to my left, Dr. Claude Lenfant, Director of National Heart, Lung and Blood Institute; Dr. Francis Collins, Director of Human Genome Research Institute; Dr. Kenneth Olden, Director of National Institute of Environmental Health Sciences; Dr. Paul Sieving, Director of the National Eye Institute. To my right, Dr. Lawrence Tabak, Director of National Institute of Dental and Craniofacial Research; Dr. Patricia Grady, Director, National Institute of Nursing Research; Dr. Donald Lindberg, Director of National Library of Medicine; and, fi-

nally, Dr. Raynard Kington, Acting Director, National Institute on Alcohol Abuse and Alcoholism. And with us, as usual, is Mr. Kerry Weems from the department whom we are pleased to have. I will call on each of them in turn. Dr. Lenfant.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Statement of the Acting Director, Dr. Ruth L. Kirschstein
House Appropriations Subcommittee on Labor-HHS-Education
April 19, 2002

on Disease Prevention and Health Promotion
accompanied by

Dr. Claude Lenfant, Director, National Heart, Lung, and Blood Institute (NHLBI)
Dr. Francis Collins, Director, National Human Genome Research Institute (NHGRI)
Dr. Kenneth Olden, Director, National Institute of Environmental Health Sciences
Dr. Paul Sieving, Director, National Eye Institute (NEI)
Dr. Lawrence Tabak, Director, National Institute of Dental and Craniofacial Research (NIDCR)
Dr. Patricia Grady, Director, National Institute of Nursing Research (NINR)
Dr. Donald Lindberg, Director, National Library of Medicine (NLM)
Dr. Raynard Kington, Acting Director, National Institute on Alcohol Abuse and Alcoholism (NIAAA)

OPENING STATEMENT OF DR. RUTH L. KIRSHSTEIN
PANEL – DISEASE PREVENTION
APRIL 19, 2002

Mr. Chairman, Members of the Committee,

At this last panel session, we again want to tell you how pleased we are to have had these opportunities to present our NIH programs and to end the continuum of presentations with a discussion of Disease Prevention and Health Promotion. In this area as in all the others, each of the Institutes has a major role in not only doing research but in communicating the results of the research. In fact, communication is the critical link between the scientific knowledge we uncover and preventing disease, maintaining healthy lives and managing chronic diseases and conditions.

These research and communication activities must be carefully coordinated among the NIH Institutes and Centers, among these Institutes and Centers and other agencies such as the Centers for Disease Control and Prevention, the Food and Drug Administration, the Substance Abuse and Mental Health Services Administration, and among all the agencies of the Federal Government, NIH, DHHS, USDA, the National Science Foundation, etc. Examples of programs related to disease prevention and health promotion carried out by the Institutes represented on this panel are:

- The National Heart, Lung, and Blood Institute's (NHLBI) successful National High Blood Pressure Program dates back to 1972. By developing messages that reflect the most current scientific information and are broadly endorsed by the medical community, this program serves as a model for patient and public education. It has helped changed the way we treat and prevent high blood pressure in this country. This educational effort related to high blood pressure has been followed by the National Cholesterol Education Program, the National Asthma Education and Prevention Program and the National Obesity Education Initiative as well as programs related to education on sleeping and on heart health in women. A driving force behind these efforts is to narrow the gap between knowledge and practice. For example, therapies for literally stopping a heart attack in its track are available but only one out of 5 persons suffering such a heart attack calls 911 early enough. NHLBI has launched its new *Act in Time* campaign to address this problem.

- With the sequencing of the entire human genome almost completed, we are focusing on the fact that there are genetic contributions to virtually all diseases. The discovery by scientists at the National Human Genome Research Institute (NHGRI) of a gene involved in the risk of prostate cancer will set the stage for prevention at the level of individuals. Other discoveries can lead to the development of gene-based "designer drugs" for many common and multifaceted diseases like diabetes, Alzheimer's disease, and hypertension. In order for the public to take advantage of our new knowledge of genetics, we first need to better

equip health professionals to discuss genetic aspects of disease with patients and their families. The National Coalition for Health Professional Education in Genetics is a national effort founded by the NIH, the American Medical Association, and the American Nursing Association to promote education and access to the latest genetic information for health professionals.

- Low vision is an impairment which cannot be corrected by standard glasses, contact lenses, surgery, or medicine and which interferes with the ability to perform everyday activities. It affects primarily the growing population over 65. While lost vision usually cannot be restored, many people can learn to make the most of the vision that remains. The National Eye Institute provides educational materials on low vision, including public service announcements and The Eye Site — a traveling exhibit for use in shopping malls, aimed at helping people learn about techniques to improve their daily lives.
- Millions of Americans suffer oral health problems because of underlying medical conditions such as diabetes, HIV infection, cystic fibrosis, cancer, developmental disabilities and/or their treatments. The National Institute of Dental and Craniofacial Research (NIDCR) created the National Oral Health Information Clearinghouse to provide a resource to meet the specific information related to special care for such patients. The clearinghouse is leading a campaign to raise awareness about the oral complications of cancer therapies. Partners in the campaign include the National Cancer Institute, the National Institute of Nursing Research, and the Centers for Disease Control and Prevention. For example, one out of three cancer patients develops oral problems as a result of treatment. This can be so debilitating that patients may cut back to less effective doses or even stop treatment entirely. The education campaign is reaching oncologists, dentists, and patients with the message that proper oral care may prevent or minimize oral complications.

- Asthma disproportionately affects people who live in the inner city and people in lower socioeconomic groups. Exposure to the allergen in dust mites is an important risk factor that can be reduced by simple steps. The use of special mattresses and pillow covers in combination with weekly laundering, regular vacuuming and cleaning of carpets can reduce levels of dust mite allergies. This simple message is being provided widely to people who live in the inner city by the National Institute of Environmental Health Sciences (NIEHS) and others.

- There are more than 20,000 organ transplants performed each year, and the numbers of patients and their long-term survival rates are increasing. Researchers funded by the National Institute of Nursing Research are addressing the post-transplant problems of survival. These include recognizing and managing the symptoms of rejection, enhancing the quality of life once patients leave the hospital, providing personal health education, helping patients become reemployed, and enhancing social support. Findings indicate that these interventions can result in a 50 percent decrease in re-hospitalizations, fewer

toxicities due to immuno-suppressive drugs, and a decrease of up to 21 percent in costs.

- Reliable consumer health information is available on the NIH web-site. It is updated daily and links to information on all aspects of health. ClinicalTrials.gov, for example, was established at the behest of the Congress and continues to grow, now containing information about 5,700 separate clinical trials. Usage by both health professionals and the public continues to grow and is now about 30 million hits a year.

- The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is concentrating much of its efforts on abusive drinking among high school and college students. Later in this hearing, we will tell you about data just released and about plans to widely inform the nation of the enormous dangers of such abuse. These plans involve college presidents, spouses of government officials at the Federal, State and local levels, as well as students themselves and private foundations.

The panel members with me today are:

- Dr. Claude Lenfant, Director, National Heart, Lung, and Blood Institute (NHLBI)
- Dr. Francis Collins, Director, National Human Genome Research Institute (NHGRI)
- Dr. Kenneth Olden, Director, National Institute of Environmental Health Sciences
- Dr. Paul Sieving, Director, National Eye Institute (NEI)
- Dr. Lawrence Tabak, Director, National Institute of Dental and Craniofacial Research (NIDCR)
- Dr. Patricia Grady, Director, National Institute of Nursing Research (NINR)
- Dr. Donald Lindberg, Director, National Library of Medicine (NLM)
- Dr. Raynard Kington, Acting Director, National Institute on Alcohol Abuse and Alcoholism (NIAAA)

I will call on each of them in turn.

Mr. Chairman, Members of the Committee,

This is the last hearing of the NIH related to the FY 2003 President's Budget. We thank you for your time, your interest, and your concerns for improving the health and well-being of the American people and the people of the world.

OPENING REMARKS—NHLBI

Dr. LENFANT. Thank you, Dr. Kirschstein, Mr. Chairman. I am very pleased to be here because this is—prevention and health promotion are truly the hallmarks of the institute program because so many of the diseases that we care for are preventable. Health education is a very powerful tool to achieve prevention and health promotion.

ACT IN TIME TO HEART ATTACK SIGNS

I would like to discuss one of our programs which is called "Act In Time to Heart Attack Signs," as it may save thousands of lives. Mr. Chairman, in the next 12 months, 1.1 million Americans will have a heart attack. For 650,000 of them, it will be the first one. For the others, it will be a repeat, maybe second or third heart attack. Of the 1.1 million patients, 520,000 will die, half of them not having reached the hospital. Why do people not go to the hospital? There are all kinds of very bad reasons for it. Frequently they do not recognize the symptoms, and even if the patient thinks they may have a heart attack, even if the doctors tell them to go to the hospital as quickly as possible, they do not get there in time. Why not? Not because the emergency personnel do not respond quickly, but because the patients just do not want to be embarrassed by having an ambulance coming to their driveway with sirens and lights or they do not want to upset their families or they are too busy to go to the hospital or they believe they will feel foolish if, after all, they do not have a heart attack. So we have started a new campaign to counteract misconceptions about heart attack signs, alleviate patients' fears, and emphasize the importance of getting treatment immediately after symptoms begin. We have developed materials such as this one that you have in front of you, actually, to help doctors to teach their patients the key messages.

First, recognize the symptoms and, second, call 911. And this material that you see here is being distributed to all parties and physicians so that they can think about those things they have to tell their patients.

But, in addition, patients do not have to wait until their doctors bring up the subject of heart attack before they can educate themselves about symptoms and develop a heart attack survival plan. We are helping them with public education programs. And I should say at this point in time the program is already successful. It has been in existence for only 6 months and the Act in Time message is now an official course of the American Red Cross which publicized and institutionalized a program, and the National Council on the Aging is also offering classes in more than 1,000 senior centers throughout the country.

We work also with the American Heart Association to distribute and diffuse information about this program throughout the whole network. Our expectation is that the Act in Time to Heart Attack Signs will be successful as many of their campaigns have been. In time I will be pleased to respond to your questions, Mr. Chairman.

[The information follows:]

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, ACT IN TIME TO HEART ATTACK SIGNS

Wallet Card: *http://www.nhlbi.nih.gov/health/public/heart/mi/wallet.htm*
Physcian Quick Reference Card: *http://www.nhlbi.nih.gov/health/prof/heart/mi/provider.htm*
Brochure: *http://www.nhlbi.nih.gov/health/public/heart/mi/core_bk.htm*

Mr. REGULA. Thank you.

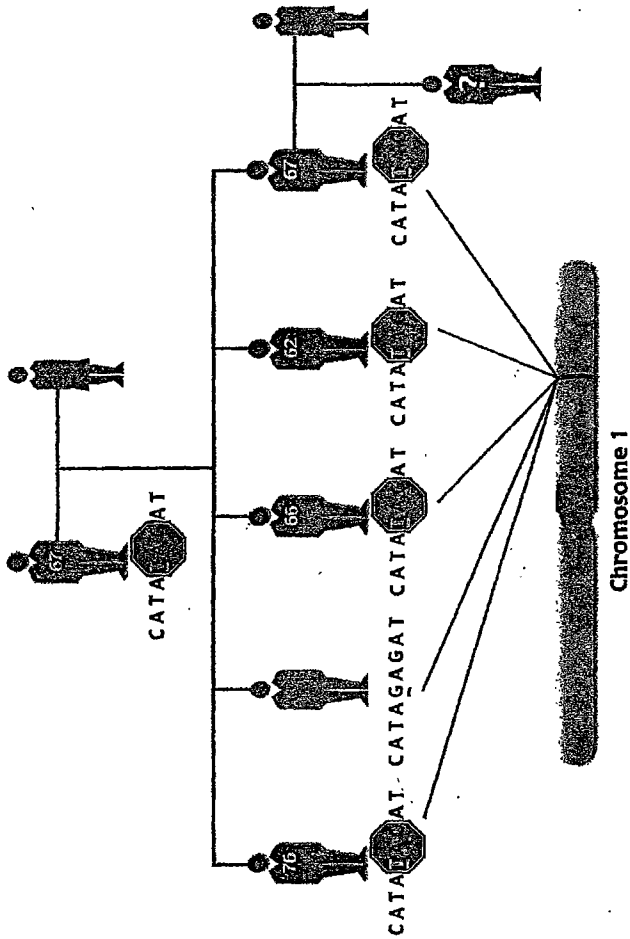
OPENING REMARKS—NHGRI

Dr. KIRSCHSTEIN. Dr. Francis Collins.

GENETICS TO DISEASE PREVENTION

Dr. COLLINS. Mr. Chairman, Mr. Obey, research on the human genome, our own DNA instruction book, is running dramatically ahead of schedule and will provide opportunities for better disease prevention and health promotion, the theme of today's hearing. Consider, the family shown on the poster. A father and four of his five sons, here marked in red, have all been affected with prostate cancer. The numbers that you see on each figure indicate the age at which each was diagnosed. Only one son, the one marked in blue, has been spared. Only a few years ago there would have been no way to track down the cause of this strong familial pattern. But now with the tools provided by the Human Genome Project, the ability to identify hereditary susceptibility factors for common disease is advancing rapidly.

[The information follows:]


CATA AT
CATAGAGAT CATA AT
CATA AT CATA AT
CATA AT CATA AT
CATA AT
Chromosome 1

Just two months ago, scientists in the intramural program of the National Human Genome Research Institute, together with colleagues at Hopkins and the Cleveland Clinic, were able to find the needle in this particular DNA haystack, a misspelling in a particular gene on chromosome one, the first gene for prostate cancer to be discovered and validated. This disease kills more than 30,000 men in the U.S. each year.

If you look under the normal individual, the one in blue, you see the normal DNA sequence, CATAGAGAT. But in the affected males, instead of a G in that one vulnerable spot there is a T. That T essentially creates a stop sign that knocks out the function of this gene. Based on this discovery, it is now possible to warn the man marked with a question mark of his potential future risk for prostate cancer, based on a genetic test.

Similar research of this sort is now proceeding rapidly to identify hereditary factors in diabetes, heart disease, breast cancer, colon cancer, Parkinson's disease, and Alzheimer's disease, to mention just a few. These advances raise the real possibility of individualized preventive medicine for all of us in the next 5 to 10 years, based on our highest susceptibilities. Perhaps even more importantly, these gene discoveries provide new treatment approaches that simply could not have been achieved otherwise.

EDUCATION IN GENOMICS

This promising future of better prevention, treatment and cure will only happen if we are preparing health care professionals and the public for this coming revolution in genomic medicine. To do this successfully, those generating health care messages and answering public inquiries must remain closely aligned with the physicians and scientists conducting this research.

Among our current products for the public are a free multimedia educational kit, which has been requested by more than 60,000 individuals, many of them high school teachers, and is now available on the web. Together with the Office of Rare Diseases, we have also just opened a Genetic and Rare Diseases Information Center. In just ten weeks this center has already handled hundreds of complex inquiries about rare diseases. Furthermore, to provide accessible, validated information about genetics to primary health care providers, doctors and nurses, we have founded the National Coalition for Health Professional Education in Genetics, in collaboration with the American Medical Association and the American Nurses Association.

This is a unique time in the history of medical research. With the availability of the sequence of the human genome in all its dazzling complexity and elegance, we have the opportunity to solve mysteries of health and disease that have vexed humankind since the dawn of time. With the support of this Congress, which has been visionary from the very beginning in seeing the promise of the Human Genome Project, the National Human Genome Research Institute will pursue an ambitious and aggressive research agenda to make those dreams come true.

Thank you very much and I will be glad to answer questions.

OPENING REMARKS—NIEHS

Dr. KIRSCHSTEIN. Dr. Kenneth Olden.

Dr. OLDEN. Mr. Chairman and Mr. Obey, complex diseases are not caused by any single factor. It is now widely accepted that most devastating diseases that plague humankind are caused by the interaction or combination of three risk factors. They are one's genetics, one's environment, and one's behavior or lifestyle. While genes may program one for a disease, when or if one develops the disease is largely determined by one's physical environment and one's behavior. Therefore, to prevent human illnesses will require identification of the various genetic, environmental and behavioral risk factors involved in the development of specific diseases. Once the risk factors have been identified, one can begin the process of studying the interaction between the various agents.

Now such information can be very important and can lead to public health or clinical prevention intervention strategies to prevent these chronic or incurable diseases. Although most of the visible environmental problems of the 1950s and 1960s have been ameliorated, massive quantities of toxic agents are still polluting our environment. Whether current levels of these exposures are contributing to the high incidence of cancer, Parkinson's, Alzheimer's, diabetes, autism, learning disabilities or other complex disorders is still a matter of considerable concern.

Take the recent determination to lower the permissible level of arsenic in drinking water from 50 parts per billion to 10 parts per billion. The policy decision is consistent with the concern that maybe ambient levels of exposures are still subjecting the American people to some risk. Also a paper was recently published by two of our grantees in the March issue of the "Journal of the American Medical Association" and it showed that tiny soot particles present in the ambient air of major U.S. cities was causing about a 12 percent increase in lung cancer.

The investment in environmental health and prevention research and translation of these results into public health policy and the practice of medicine is one strategy to eliminate the epidemic of diseases. To quote Ms. Karen Miller of the Long Island Breast Cancer Coalition, "Prevention is the cure."

Thank you for your attention and I, too, would be pleased to answer any questions you might have.

OPENING REMARKS—NEI

Dr. KIRSCHSTEIN. Dr. Paul Sieving.

EYE DISEASES—EXTENT OF THE PROBLEM

Dr. SIEVING. Mr. Chairman and members of the subcommittee, eye disease is a major health problem in the United States and causes significant suffering, disability, loss of productivity and diminished quality of life, particularly for our elderly citizens. A report issued by the National Eye Institute just a few weeks ago showed that more Americans than ever are facing the threat of blindness from age-related eye diseases. More than 1,000,000 Americans age 40 years or older are currently blind and another 2.4 million are visually impaired, and as Americans are living

longer and generally healthier lives, vision problems associated with aging can be expected to grow substantially in the future.

PROMOTING EYE HEALTH

In response to these problems, the National Eye Institute has developed programs for promoting eye health. The NEI is the lead Federal agency addressing the eye health education needs of the Nation. Our activities in this area represent a natural extension of our support for vision research. In the dissemination of research results, we translating these results into practical applications for health care professionals, for patients, and for the public, which is integral to our mission of improving the eye and vision health of our country.

In 1991, in response to a congressional mandate, the National Eye Institute established the National Eye Health Education Program, or NEHEP. NEHEP currently includes education programs targeting three areas. The first is directed toward glaucoma, a disease that damages the optic nerve of the eye and that can lead progressively to blindness.

A second program involves diabetic eye disease, a term for the visual complications that result from abnormal blood vessels that develop in the eye due to underlying diabetes.

A third program is for low vision education. Low vision is a visual impairment that cannot be corrected by standard glasses, contact lenses, medicine or surgery. Impaired or low vision interferes with the ability to perform even seemingly simple every-day activities of reading and driving or even to see the smile of a spouse. Education and practical assistance from an eye care provider can help those with low vision to optimize their remaining sight.

NEHEP is coordinated by the National Eye Institute in partnership with more than 65 national organizations representing professional associations, voluntary, civic and fraternal organizations, and other government agencies. Through this partnership, the NEI multiplies its efforts in disseminating information to the public. NEHEP also provides opportunities for the partners to collaborate on community-based programs and to implement these through their own networks. NEHEP utilizes a variety of outreach strategies, including program planning guides and reports for health professionals, public service announcements for radio, television and print media, and the distribution of educational kits.

NEHEP developed and coordinates traveling exhibits that visit shopping centers around the country, thereby reaching a diverse population. The NEI also disseminates research results that impact public health. For instance, last October the Eye Institute released results of a major 10-year clinical trial showing that supplementing the diet with high levels of antioxidants and zinc substantially reduced the risk of developing advanced age-related macular degeneration, and this lowered the risk of vision loss. The NEI coordinated a national and locally-based dissemination process so that over 174,000,000 people had the opportunity to learn about these important results through print, radio, television and Internet coverage.

Further, a public vision information network coordinated by the NEI assisted in disseminating these results nationwide. With these

efforts, the National Eye Institute is playing a valuable role in placing vision on the public health agenda and bringing the importance of vision and eye health to a broader community.

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

Mr. REGULA. Thank you.

Dr. KIRSCHSTEIN. Dr. Lawrence Tabak.

OPENING REMARKS—NIDCR

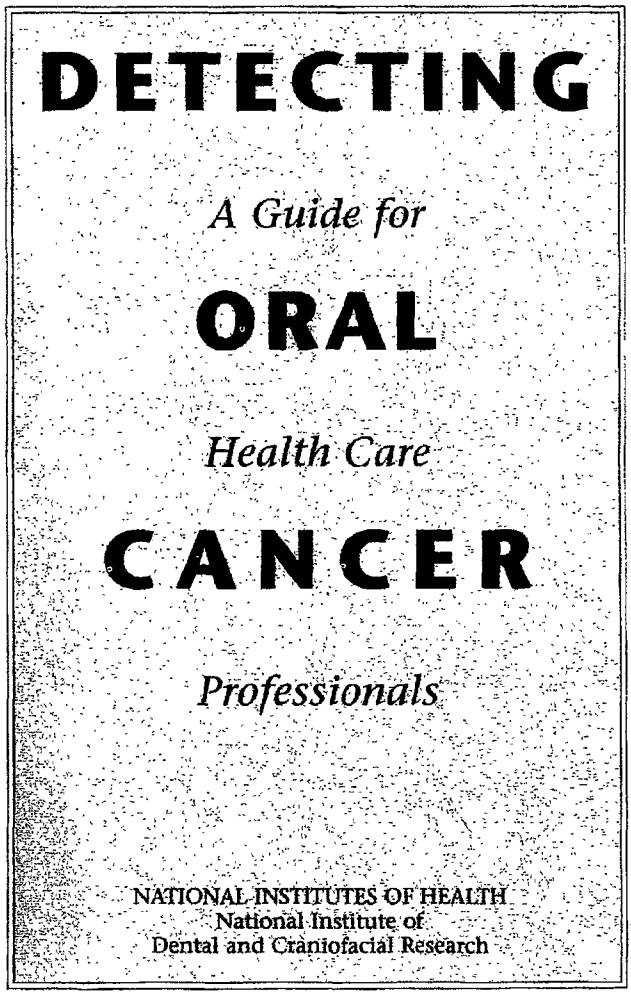
Dr. TABAK. Mr. Chairman and Mr. Obey, I am pleased to appear before you on behalf of the National Institute of Dental and Craniofacial Research. Our Institute was founded 54 years ago on the principle of prevention. Indeed, the prevention of dental decay by water fluoridation has been hailed as one of the top 10 public health achievements of the 20th century. Today our Institute's disease prevention efforts are quite broad, including our continuing efforts to prevent dental decay in at-risk patients.

ORAL CANCER EXAMINATIONS

However, today I will focus on NIDCR's ongoing efforts to increase public and professional awareness of oral cancer and the need for oral cancer examinations. The poster to your left demonstrates how to perform an oral cancer exam, and this was sent to 145,000 practicing dentists and dental students as part of the special issue of the "Journal of the American Dental Association" that you have in front of you. Only 20 percent of adults in the United States reported ever having an oral cancer examination. The fact that so many Americans are not receiving this 90-second painless examination is disturbing because, unlike other cancer sites, the mouth, head and neck are readily accessible. Yet half of all oral cancers go undetected until it is too late. Five-year survival for these cancers is among the lowest of all major cancers and it is worse for blacks than for whites.

[The information follows:]

The brochure identified below was utilized as a chart at the hearing. A full brochure can be found on the Internet at the following URL: http://www.nohic.nidcr.nih.gov/pubs/detect/index.html



During this decade an estimated 74,000 Americans will die from oral and pharyngeal cancer. Thousands more will undergo multiple surgeries to remove advanced tumors and to reconstruct their faces. Through increasing awareness about oral cancer prevention, we can make early detection the norm, never the exception.

Recently we funded five states—New York, North Carolina, Florida, Michigan, and Illinois—to develop models of oral cancer prevention and early detection. These grants will enable them to tailor intervention strategies to each state's specific demographic and professional needs.

In tandem with its outreach efforts, NIDCR has invested in research to develop powerful new tests for the rapid diagnosis of oral cancer. NIDCR's scientists are defining the molecular signature of cells undergoing the earliest cancerous changes. These signature molecules can be detected in oral fluids, thus forming the basis of a simple noninvasive diagnostic test. NIDCR is currently supporting a research initiative designed to exploit the use of oral fluids for detection of a broad range of infectious agents as well as harmful chemicals.

To conclude, I invite you to give the booklet, "Detection of Oral Cancer," which is inserted in that journal I gave you, to your own dentist during your next appointment; and if you have not yet had an oral cancer examination, ask your dentist to do so.

Thank you for the opportunity to speak with you and, of course, I would be pleased to answer any questions.

Mr. REGULA. And we can charge him for that professional advice; is that correct?

OPENING REMARKS—NINR

Dr. KIRSCHSTEIN. Dr. Patricia Grady.

Dr. GRADY. Mr. Chairman, Mr. Obey, as of this year, our 15th anniversary, NINR-supported research is providing a scientific basis for patient care that is used by the many disciplines among health care professionals, especially by this Nation's 2.7 million nurses. Our research studies in health promotion and disease prevention include the effects of diet and exercise programs on both healthy and ill people, ways to reduce risky behavior, and ways to prevent or reduce the impact of illness. Let me give you four examples.

POST-TRANSPLANT PROBLEMS OF PATIENTS

With the number and longevity of organ transplant patients increasing, nurse researchers are addressing the post-transplant problems related to survival once patients leave the hospital. The programs of research focus on recognizing and managing the symptoms of rejection and promoting quality of life. After one year, study findings indicated a 50 percent decrease in rehospitalization for infections and fewer immunosuppressive drug toxicities for these patients. Costs were also decreased by 21 percent.

CESAREAN DELIVERY INCREASES RISK OF UTERINE RUPTURE

Another example is that of a recent study published in the New England Journal of Medicine demonstrating that cesarian delivery

can increase by three times the risk of uterine rupture during labor in a subsequent pregnancy. If drugs are used to induce labor, the risk increases 15-fold. Since 60 percent of women with prior cesarian deliveries attempt labor with the next pregnancy, it is important that this information be incorporated into patient education.

REDUCING LEAD POISONING IN THE COMMUNITY

Third, a major health problem in both rural and urban communities is the issue of lead poisoning. Investigators formed a partnership with an academic nursing center and a community consisting primarily of African-Americans. Analysis of the data following an education and awareness program indicates a decrease in lead levels of the study group by 11 percent. This program has received the National Environmental Education Achievement Award.

NATIVE AMERICAN TALKING CIRCLES TO REDUCE DIABETES

And, finally, you may have seen last week a Washington Post article on our community-based study using Talking Circles for rural native American tribes with diabetes in South Dakota and Nebraska. Native Americans are about three times more likely to develop diabetes, and the condition is often related to a high fat diet and insufficient exercise. In this study, Talking Circles, which capitalize on the oral tradition of story-telling in group settings, were used to discuss prevention strategies and avoidance of risky behaviors. After findings indicated a change in attitude toward diabetes and improved health outcomes, the research has now been translated to practice. The communities are continuing the Talking Circles and incorporating healthy diet instruction and blood sugar testing.

Another outcome is the development of a cookbook that combines a controlled diabetic diet with traditional foods such as buffalo and rice soup.

In conclusion, NINR and the investigators we support strive through dissemination to make benefits of nursing research available, including successful interventions and novel uses of technology. Incorporating positive results such as these will make a long-term difference in improving the health of our Nation's people. Thank you.

OPENING REMARKS—NLM

Dr. KIRSCHSTEIN. Dr. Donald Lindberg.

Dr. LINDBERG. Mr. Chairman, Mr. Obey, NLM's major mission is to acquire, organize, and disseminate the biomedical knowledge of the world for the benefit of the public health, so we are intimately involved in the mission of preventing disease and promoting health. Increasingly the dissemination occurs via the worldwide web and Internet, and we have a display of this home page. It merely is there so we can show you that one can go from that one display either in the direction of helping a doctor to get information to treat a patient or in the direction of a researcher to follow up a discovery in the scientific literature or to the consumer, which increasingly is an important user of this information. So, of course, increasingly the dissemination occurs in this method, but increas-

ingly the discoveries come from NIH institutes and the grantees that they fund.

In the case of the health professional, he or she has to deal with the fact that 500,000 articles every year are published on these discoveries. So you need a computer to find your way to exactly the right one. This particular display also shows that it links to—in this case we chose the example of macular degeneration, but it links to Online Mendelian Inheritance in Man at John Hopkins, the genetic information.

In the case of the display in the middle on the bottom, the patients are the beneficiaries, and starting in 1997 this committee and its comparable committee in the other chamber gave us encouragement to try to serve patients' families and the public directly. We had formerly tried to do this only through the health professional. By 1998 we had already made an arrangement so that the searching could be essentially free and we had dropped the requirement to know the identity of the person giving the search. Both of those are essential if you are going to serve the public. And we found to our amazement that within the first year, 10 times the number of searches were done, from 7,000,000 to 75,000,000, a third of them by members of the public. So we created a new database, Medline Plus, for the public and this has had very, very heavy usage. There is not time to go through all of these things, but I would like to say that the NLM serves the public by collaboration with colleagues at NIH. The NIH institutes are, of course, the first place we look for this kind of information although we select information that is well understood by the public and well presented, also nationally linked to VA and CDC and other HHS agencies as well as voluntary health organizations.

Again the linkages are what is important so that whether it is the doctor, the patient or the clinician, we can link to clinical trials, another requirement happily given by the Congress and the FDA Modernization Act in 1997, so that all of the people really can share the same information.

It is sort of a point-and-click world we are all living in, and that is literally the case that when you enter this home page. You can as a patient go to what you want to know or a dictionary to help look at it, or an encyclopedia on line to understand it, or a tutorial say on anthrax. In the same session a doctor can go to the article he wants to find to treat a patient. A researcher can go sort of over on the other side on the right where you see diagrams and maps of where is the gene or genes in this case associated with macular degeneration and which are the coding regions, and the whole detail of that business is available in the same site at the same time and through the same organization, and of course once again I echo my colleagues in saying we are grateful to the Congress for both the leadership and the support.

[The information follows:]

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Thank you.
Mr. REGULA. Thank you.
Dr. KIRSCHSTEIN. Dr. Raynard Kington.

OPENING REMARKS—NIAAA

Dr. KINGTON. Mr. Chairman and Mr. Obey, alcohol abuse and alcoholism are prevalent and costly disorders in the United States. More than 14 million Americans abuse alcohol or are alcohol-dependent, and alcohol problems cost society $185 billion annually. The consequences of these disorders are preventable.

We base preventive interventions on our growing understanding of the biological, psychological, and environmental factors that contribute to the risk of developing alcohol use disorders. Our prevention research portfolio ranges from studies of individuals to studies of communities.

PREVENTION OF ALCOHOL ABUSE

For example, at the individual level we are designing and testing interventions to prevent convicted drunk drivers from repeating their offenses. Another example involves community-wide studies that are examining whether policy changes result in more responsible alcohol service by bars and restaurants.

Our data indicate that some populations, however, require special focus. Among them are college students. The NIAAA Task Force on College Drinking recently issued its recommendations on the prevention of abusive drinking by college students, accomplanied by a number of additional research and outreach projects. I have a graphic that illustrates the range of educational material our Task Force on College Drinking has generated, including material targeted to parents and residential advisors. Our web site in the example, received over 650,000 hits in its first week, and our outreach information will be mailed to every college president in the United States. Our newly funded Multi-Campus Alcohol Problem Intervention Program, on 16 campuses of two California university systems, is just one example of the kinds of research projects that we are supporting in this area.

Abusive drinking among youth extends well beyond the college population, however, and we now co-sponsor, with the Robert Wood Johnson Foundation and other Federal Agencies, the Leadership to Keep Children Alcohol-Free Initiative. Thirty-three governors' spouses have joined this effort to prevent children between the ages of 9 and 15 from drinking. We also fund a major community-based intervention research project, which is testing among urban youth a community intervention that was effective in reducing underage drinking in rural populations. In addition, our investigators are examining the effects of advertising on youths' attitudes and perceptions about drinking.

Our prevention research on fetal alcohol syndrome, the leading cause of preventable birth defects, now focuses on women in minority groups at risk. Overall, we support 10 fetal alcohol syndrome prevention research projects. We recently began a pilot public-information project in the District of Columbia, which targets African-American women.

We also conducted the fourth annual National Alcohol Screening day, in the general population, just last weekend. This program promotes the use of proven, effective, brief questionnaires to identify persons at risk of alcohol abuse and refers those at risk for further evaluation and treatment.

It is important to note that some of the risk of developing alcoholism is genetic. While we conduct behavioral preventive research, our basic-science investigators are seeking genetic and molecular markers that will tell us who is most at risk, and biologic factors that we can target, to form our prevention and treatment strategies.

In summary, prevention, research, and health promotion are critical to the NIAAA mission. As we develop new knowledge, we are able to design more effective programs for preventing the consequences of alcohol abuse.

Thank you.

Mr. REGULA. Thank you. Dr. Kirschstein, I believe this is your last hearing, am I correct?

Dr. KIRSCHSTEIN. Yes, sir.

Mr. REGULA. You have given wonderful service to the Nation and providing leadership for NIH. I think in many respects NIH is somewhat of a well-kept secret among the general public. Their lives are improved in many ways by work that is done there and the leadership you have provided, and most people, unless they really have a critical illness, they do not necessarily realize that what they are getting by way of medical services is an outgrowth of the research that has been done at NIH, and I know that the Congress is committed under your watch, in part at least, to doubling the budget. So I think that says very effectively the confidence that the Members of Congress have in the work that is now being done by NIH.

We wish you well and we want to say we appreciate what you have done in providing leadership for the agency.

Mr. Obey, would you want to comment?

NIH FUNDING

Mr. OBEY. Well, I do not think I am going to take the floor to disagree. I simply want to say that, Doctor, I think you have provided wonderful service to the country and wonderful leadership to NIH, not just in the two times that you have served as acting director, but most importantly in all of the time that you have served in other capacities. I think it is safe to say that funding for NIH has become one of those activities which is popular on Capitol Hill. When I came to this Subcommittee, we were having an argument between President Nixon and Senator Kennedy about who would provide the most money for NCI and the money that was provided to NCI was terrific. The problem is that it came at the expense often of the funding for other institutes. I think the main task through the years that you have had on that side of the table, all of you, has been to convince politicians to learn as much as we can about what it is you do without putting our cotton-picking hands on the decision-making process and trying to decide for ourselves where the dollars ought to actually go in fighting one disease versus another. Politicians like to claim expertise in every field.

They ain't got it. And I just want to thank you especially for the effort that you expended to help Congress play its proper role in the oversight of NIH without going to meddling. Thank you for everything you have done.

Dr. KIRSCHSTEIN. Thank you, sir. My colleagues and I look forward to visiting both your district and Mr. Regula's district in early May.

Mr. OBEY. I am looking forward to that, too. It is one of the few bipartisan activities that will occur around here this year, I am afraid. But, nonetheless, I am looking forward to going to Ralph's district and I hope he is looking forward to coming to mine.

ALCOHOL ADVERTISING

Mr. REGULA. We are. Good health does not have a label, R or a D. Good health is something all of us want and, Dr. Kirschstein, we wish you many good years of health. You know all the rules, I am sure, to stay that way, and you know where to go if you need professional advice prospectively.

A few questions, and then I am sure Mr. Obey has some likewise. Dr. Kington, I read a lot of the advertising by the industry, the alcohol industry, and they claim that they are doing a lot in preventing teenage drinking and the proper use of alcohol. What would your evaluation be of the industry efforts? Are they for real?

Dr. KINGTON. We are supporting a number of research projects that are assessing the impact of advertising on behavior. Already, a substantial amount of evidence suggests that alcohol advertisements can affect attitudes and expectations. We are not as sure about whether or not it actually affects behavior, but we have a number of studies, ongoing now, that will give us more information. We are especially concerned about advertising that targets people younger than 21, because it has the potential to influence underage drinkers, who should not drink under any circumstance.

Mr. REGULA. So you think the advertising done by the private sector alcohol industry has some value?

Dr. KINGTON. Which advertising are you referring to?

Mr. REGULA. In other words, to try to make people responsible in the use of alcohol.

Dr. KINGTON. We know that some forms of social marketing advocate responsible behaviors of all kinds, including responsible alcohol consumption. To the extent that social marketing efforts are appropriately targeted and designed, they hold the potential to influence behavior. Of course, the extent of social marketing must be viewed in the context of all the other advertising that favors alcohol consumption. The goal is to advocate responsible consumption of alcohol.

FLUORIDATION

Mr. REGULA. Dr. Tabak, when I was in the State legislature, fluoridation was a big controversy. Has that pretty much gone by the board and the efficacy of fluoridation and prevention of dental problems is a given in today's world?

Dr. TABAK. Certainly in our world it is a given, Mr. Regula. Community water fluoridation benefits millions of Americans. For over half a century it has helped improve the quality of life through re-

duced pain and suffering related to tooth decay, reduced tooth loss, reduced lost time from school and work and less money spent on dental care. One of the significant advantages of water fluoridation is that anyone, regardless of their socioeconomic level, can enjoy its benefits during their daily lives, and so within the United States, fluoridated water is the most cost-effective method for eliminating tooth decay.

Mr. REGULA. I noticed many people, of course, live where they have wells, but now I think you could buy bottled water that is treated with fluoridation additives to overcome the fact that you are not in a city system.

Dr. TABAK. There is no question that many persons use bottled water. Interestingly enough, though, many of the bottled waters have no fluoride at all, and particularly when there are young children involved, you have to assess that because there might be a need for fluoride supplements.

Mr. REGULA. If you do not get it in the water.

Dr. TABAK. If you do not get it in your water or if the bottled water that you are using is lacking it as well.

Mr. REGULA. The staff just handed me a note here. Dr. Kirschstein, I see you were very much involved in the selection of the Sabin vaccine for public use in eradicating polio?

Dr. KIRSCHSTEIN. Yes, sir.

Mr. REGULA. It has been a real success story, has it not?

Dr. KIRSCHSTEIN. Yes, sir. But we have to watch out. If you saw the Wall Street Journal this morning——

Mr. REGULA. I saw that article.

Dr. KIRSCHSTEIN [continuing]. There is an article that says that perhaps the polio that has been seen in the Caribbean, the island of Hispaniola, is a result of a series of vacuumed mutations of the attenuated virus to a more virulent form. We studied that years ago because there is no question that the oral vaccine is excreted for what we consider to be a very long time. I thought a year or so was sufficient after vaccination; however, the article refers to the fact that there has been a man down there, at least one that they found, who has been excreting the virus since 1995. That is, to my knowledge, a record. And CDC and, I assume, my colleagues in the organization that I used to work for which regulates and licenses polio vaccine are studying this. I said in the car coming down to my colleagues that it may be we want to go back into the lab.

Mr. REGULA. Perhaps you will get that opportunity.

Dr. KIRSCHSTEIN. Perhaps I will.

EYE HEALTH AS INDICATOR OF OVERALL HEALTH

Mr. REGULA. Dr. Sieving, I was interested in your comments on eyes. I remember reading somewhere that the eyes are the window to your health, that you can identify a lot of other health problems by examining the eyes. Is that an accurate statement?

Dr. SIEVING. I think that is a fair statement and an important statement. The eye is a complex organ. The eyeball has blood vessels and nerve cells and supporting cells, and many of the diseases that affect us systemically end up showing up in the eye. If one goes back in history a hundred or more years, at a time when it

was not possible to look at blood vessels directly in the heart as it is today, for example, one could still look at the blood vessels in the eye. Observing the health of the eye has been one of the ways in which medicine has progressed and health care has progressed. And the eye continues to be central to us as people. It is a social organ. It is also a medical organ that gives us insights into some basic biological principles.

EYE TREATMENATS TO CURE BLINDNESS

One of the very interesting things that happened this last year concerned treatments that appear capable of restoring vision in eyes that are blind. The eye is a very accessible biological target for trying out some of the most advanced therapies that we have, including work such as in gene transfer.

COUNCIL ON AGING

Mr. REGULA. Dr. Lenfant, am I saying that correctly? This is interesting material. Do you think it would be practical to get the AARP to put these in their mailers? This little pamphlet on heart attack, it seems to me, it would be very valuable to be in every household.

Dr. LENFANT. Yes, indeed. As I mentioned earlier, we are working with the Council on Aging, which is an organization that has similar goals with AARP. What the Council on Aging has that the AARP does not, the AARP works with the individual; the Council on Aging works with organizations where you have a large number of elderly, assisted living and whatever. So we can, by going there, set up a system to have teaching to the subject, to the people who are there and basically say, you know, you feel this way or that way this morning, pay attention to that, and go see the nurse in that establishment, go see the doctor in that establishment, and they will take you to the hospital if it is needed. So we are expanding that network, as I mentioned.

We started this program about seven months ago, and I think so far we have made quite a reasonable progress to reach out there, especially in the elderly population which is, of course, the population where cardiovascular events, sudden cardiovascular events are more frequent.

Mr. REGULA. It seems to me that that could be in everybody's household.

Dr. LENFANT. That is what we would like to do.

Mr. REGULA. And something similar on stroke, because I always hear that the quicker you can get somebody to the hospital, the more likely the remedial success on strokes, which goes with this.

WORK WITH PHYSICIANS, THEN PATIENTS

Dr. LENFANT. As I said earlier, we have a two-pronged attack, one of which is to work with the physicians, general practitioner, so that in turn they can speak to their patients, and then we go directly to the patients to make them realize that there is no reason to be ashamed to pay attention to a chest pain or whatever and do something about it.

Mr. REGULA. Well, in all your testimony I hear the need to get the information in the hands of the public. Now do each of you have a web site? What kind of usage do you get in the terms of the public accessing the web sites? Maybe you could speak for the group.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS

Dr. KIRSCHSTEIN. Each of the institutes has a web site and, in addition, the NIH as a whole has a web site as well. We not only get tremendous usage, but we have been cited repeatedly by organizations that do the survey as having the most accessible web site, a web site that has more hits than almost anything except perhaps the Internal Revenue Service. In the last few days, the Internal Revenue Service has exceeded us, but up until then perhaps we exceeded it, and a web site that provides useful information. We are constantly bringing it up to date and improving it.

In the NIH web site we highlight new discoveries so they can click on immediately to them and learn what is what. We have an excellent search engine. And my colleagues might like to add to that.

NHLBI COMMUNICATIONS NETWORK

Dr. LENFANT. We have throughout the network, where actually we have 6,000 sites in all the 50 states where we communicate immediately the kind of information which is important that the public should know and hear about, and in turn the sites of this network distribute this information in the communities where they are located.

Mr. REGULA. What is the code to get onto the NIH web site?

Dr. KIRSCHSTEIN. www.NIH.gov.

Mr. REGULA. That is very simple, easy to remember.

Mr. Obey.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS

Mr. OBEY. Thank you, Mr. Chairman. Dr. Collins, as I sit here listening, and as I went down earlier today to see a display set up by the National Federation for the Blind, I was struck again by the disparities that we have in this country in the healthcare field, and it just seems to me that every dollar that we invest in medical research increases the immorality of having a healthcare system that does not guarantee affordable access to health care to everyone. That means that every time we learn something new, what we are depriving some of our citizens of becomes more and more important, and the gap between the health haves and the health have-nots becomes even more important with every single thing that we learn, thanks to the taxpayer dollars that are invested in NIH. That is why, as you know, I have been concerned for years about whether or not as we unravel the mysteries of the human genome our actions on the legal and ethical front will keep pace with what we learn on the scientific and medical front. As you know, 5 percent of your budget is devoted each year to try to deal with and study the ethical and legal and social implications of the knowledge that we gain from the human genome project. We have a high risk

of discrimination, both by employers who may not want to hire somebody if they learn that they have a genetic predisposition to a specific disease, and insurance companies who certainly may not want to insure those same people. That, in my view, creates an even greater moral obligation on us.

What I would like to ask you is how have you used that 5 percent over the years? What have we gotten? What are we getting for those dollars? What do you most worry about in that area, and what do we need to do as policymakers in order to see to it that the bright side of the knowledge that we gain from the human genome project does not produce a dark side in terms of unfair treatment of persons who are found to have disposition to one disease or another?

Dr. COLLINS. Mr. Obey, that is a wonderfully eloquent statement of the issues that we have been wrestling with since the human genome project was founded some 12 years ago in the ethical, legal and social implications program called ELSI program. This is a new experiment where we are funding research on the ethical, legal and social consequences of a scientific enterprise at the same time that we are pursuing the science, as opposed to the usual historical situation where you wait for the crisis, and then try to figure out what to do. I think this has been a successful experiment in that we have a wealth of analyses and elegant scholarship. We have recruited into this field legal scholars, social scientists, ethicists, theologians, and others who are making their careers out of analyzing these issues and making recommendations about what should be done. And through that effort we have really nailed down the major immediate priorities of policy decisions that need to be made.

GENETIC DISCRIMINATION

Dr. COLLINS. When I came to NIH some 9 years ago, I knew I was coming to lead a project to try to unravel the human instruction book. I was unprepared for how much of my time would end up being devoted to these ELSI issues, but I really should be spending even more time, because if we don't get these right, then all of the scientific advances will not necessarily benefit the public.

So what do we need to do? Frankly, my frustration, Mr. Obey, is that we do now have the scholarship. We do have the research. We have identified and defined the issues and developed possible solutions. But in areas that are most ripe for a solution, the solution requires Federal legislation. It is difficult for me and my colleagues and the ELSI researchers to make sure that that happens.

Most prominent right now is the issue that you described very accurately, about the risk of genetic discrimination. This is not a hypothetical situation. There are people who have had their health insurance taken away or who have had their jobs taken away because they were found to be at risk for some future illness based upon genetic information. That is not just. It is also not workable, since we all have glitches in our DNA, and if that becomes a reason to lose your job, well, we are all going to lose our jobs. There are no perfect specimens, even in the United States Congress.

And so what should be done? Well, it is pretty straightforward, and more than two dozen States have actually acted upon this. We

need effective Federal legislation to prevent the use of predictive genetic information when it comes to health insurance and to employment decisions. I am very happy to say that in the Senate there are bills from both the Democratic and the Republican Party that address this issue quite well and have only modest differences between them. President Bush last summer spoke out strongly in favor of the need for such legislation, and the White House has continued to endorse that. But several months have gone by since those positive steps, and we have not yet seen a bill actually come up for a vote in the Senate—Nor, frankly, has there been much activity in the House for a while.

This is such an important issue. It is already an issue for people who are asked about their interest in participating in research. Research these days often involves genetic analysis. People are afraid to be part of genetic research. Even though they want the information, they are afraid information about them might leak out and they might find themselves without medical coverage. That is the number one reason why people decide not to participate in a number of our research protocols.

We are missing out on the chance to learn more about genetics because of this fear, and I am afraid the solution really then does need to engage the political system. I hope that this is the year where appropriate legislation is finally passed.

There are a number of other issues, that need attention. I could go on, and you probably can tell that I am starting to.

Mr. OBEY. Please do. It is nice to see action coming from somewhere.

GENETIC TESTING

Dr. COLLINS. We need better oversight for genetic testing to be sure that such tests are well-validated before they are offered to the public. The Secretary's Advisory Committee on Genetic Testing is a direct outgrowth of the ELSI program. The Committee, has been debating long and hard about issue this and have recommended that genetic testing requires additional governmental oversight, ideally from the FDA, and those recommendations are being evaluated.

The whole question of how to carry out research in an ethical way when it involves genetics has been much debated issues include what kind of consent do you need and what kind of privacy protections do you need. We have made remarkable progress in these areas and there is a general sense of what the principles should be, though these have not yet been completely implemented.

And finally, the ELSI issue that undergirds all of this is education, which is our topic today: If the public is unprepared for the complexities of genetics or if health professionals are unprepared to begin to practice this kind of medicine, then we may end up with a very confusing outcome where really valuable information does not find its way into rational health behavior decisions. We have to work very hard to prepare all sectors to be ready for this new area of healthcare.

Mr. OBEY. Well, I thank you, and I think that is a terrific statement, and I hope that Congress pays attention to it, because it seems to me that the more you learn and the longer it takes us to

pass something, the more difficult it is going to be to pass something, because people will have higher and higher stakes in resisting the kind of legal protections that, in my view, are morally crucial.

RESEARCH GRANTS

Dr. COLLINS. You are quite right.

Mr. OBEY. Dr. Olden, in looking at your budget at the Environmental Health Sciences Institute, it is my understanding that the overall number of research grants at your institute, both new and renewal, will go down by about 7 percent, and the number of new research grants declines by about 25 percent. Is that right?

Dr. OLDEN. That is correct.

Mr. OBEY. Looking at it another way, I understand the success rate for applications at NIEHS is below the NIH average, 27 percent to 31 percent.

Dr. OLDEN. That is correct.

Mr. OBEY. What is going on here? Why that drop? I mean, that certainly seems startling to me.

Dr. OLDEN. For one thing the cost of individual RO1 grants is going up, and I think in our Institute, we estimate that the cost will go up about $50,000 per year. The other issue is that because of the publication of the first draft of the human genome, a lot of opportunities have been made available to environmental health scientists and toxicologists, so we have undertaken some new efforts through mechanisms other than individual RO1 grants. For example, we started an Environmental Genome Project, we started a Toxicogenomic Center: these are resource-intensive—and recently we have created a Mouse Genome Center. We are not using the investigator-initiated mechanism to generate interest in the scientific community in those efforts. So that is, in part, the explanation.

We are taking on proteomics as another major effort, and so we are addressing, in a sense, big science issues to respond to the scientific opportunities and challenges made available by the cloning of the human genome.

Mr. OBEY. But that large drop in the number of new research grants, that is not duplicated across the board in NIH's budget. I guess I don't understand why has that particular impact here and not in the other institutes.

Dr. OLDEN. Well, I really think the scientific opportunities in environmental health sciences and I don't say this to my colleagues here—probably exceed that in any other institute in the NIH, and they are made possible by the revolution of human genetics and the human genome database.

One thing that I know I have talked with you about is the capacity to develop new, more economical, fast and informative carcinogenicity test systems—test systems that can identify carcinogens in a matter of weeks, not years, and at a cost of $2 to $6 million per chemical. So we are making investments in this area. It is a big area. It involves toxicogenomics, metabonomics and proteomics, and these are big science projects.

Even though the grant goes to one person, it does involve a lot of scientists in an institution. So I think the number of scientists that are involved in our science is much greater than it ever has

been, in spite of the fact that our absolute numbers next year will go down.

Mr. OBEY. Well, I have two other questions I would look to ask you for the record——

Dr. OLDEN. All right.

ORAL HEALTH DISPARITIES

Mr. OBEY [continuing]. Because I don't have time, and I would like to turn to Dr. Tabak for my last question on this round.

And let me simply preface my question by telling you a story. The data I had been the most angry in all of the 33 years that I have spent in this Congress was the day that I went to a community in my district to announce a small grant to establish a roving dental clinic for four lower-income counties, and when I announced that grant—and there were a number of people there—there was one woman there who told me her story, and essentially her husband had been very sick for a long period of time. She had a son who had had braces on his teeth forever, and in that four-county area we had, I think, 67 dentists, and only 34 of them took Medicaid patients because of the horrendously low reimbursement rate that is provided. And so she called almost all of the dentists who did take Medicaid patients and could not find a single one who would remove that boy's braces. So finally she held the kid down while the father took the braces off with a pair of pliers.

Now, you can't do anything about that. On this side of the table we ought to be able to do something about that. I just want to ask you what is your understanding of the pattern of dental neglect that we see as it is distributed across America's children? What information do you have that could tell us what percentage of dental needs of well-off families are being met in comparison to what percentage of dental needs are being met for persons who are, for instance, at the Medicaid income level in this country? What do you know about what the national pattern of disparity is with respect to dental care for children?

Mr. REGULA. Would you yield?

Mr. OBEY. Sure.

Mr. REGULA. I wonder if you would include in that answer to Mr. Obey's question the Indian population, because it is my understanding that there is a severe lacking for dental care.

Dr. TABAK. Well, certainly each of you speaks to a very important issue. There are health disparities and certainly oral health disparities. In particular dental decay has become increasingly polarized. That means that fewer children account for more and more of the burden of disease, and in part that relates to socioeconomic status. In part that relates to access to care, which Mr. Obey has mentioned. And so our response at NIDCR is to support the research that will help prevent the decay or disease from ever occurring.

In particular, with regard to American Indians and Alaskan Natives, NIDCR has been working together with the National Institute of General Medical Sciences and the Indian Health Service in their so-called NARCH program; that is, the Native American Research Centers for Health. And we recently funded one of the projects in the Northwest Portland Indian Health Board NARCH,

which specifically relates to early childhood dental decay among the Northwest Indian populations. We also have a center in the Northwest Alaskan Center to reduce oral health disparities with research focused on understanding dental fear, understanding the natural immunity that individuals have against oral disease, and transmission of the microorganisms which cause dental decay from caregivers. And so it is through studies of these types that we hope to be able to reduce and eventually eliminate these disparities.

Mr. OBEY. But isn't it true that just 25 percent of children now account for something like 80 percent of all tooth decay among children?

Dr. TABAK. That is correct.

Mr. OBEY. Thank you, Mr. Chairman.

Mr. REGULA. Thank you.

Ms. DeLauro.

GENETIC DISCRIMINATION

Ms. DELAURO. Thank you very much, Mr. Chairman. Let me just make one comment about the genetic—thank you. I want to make a comment on the genetic nondiscrimination issue that my colleague Mr. Obey talked about, Dr. Collins. In the House, you may know this—I don't know the extent to which everyone does—but my colleague, Congresswoman Slaughter, has had a bill for the last several years, the genetic nondiscrimination bill. I will just tell you that there are 259 cosponsors of that piece of legislation, which by virtue of the numbers means that is it is a bipartisan piece of legislation, and as I understand it, to date there haven't been any hearings on this piece of legislation, and we can't seem to get any hearings on what is a particularly critical piece of legislation for our times.

It often is the case that we can be guilty or culpable of not acting at the right time, but this is so timely given the nature of the technology that we have before us today. I say this to make you know this. As my colleague said before, this is not your doing. This is our doing here. This is our problem here. But I guess what I do is I enlist the support of the medical community and the people who are dealing with this, you know, on a daily basis that understand more than potentially, you know—that we understand how quickly the technology is moving, and that if we do not act on this genetic nondiscrimination issue, that we are—you know, we are just guilty of not doing our job here. And unfortunately we can't be prosecuted on that basis, but we have the knowledge that we need in order that we can protect individuals today from loss of insurance, loss of job or anything else so that maybe you can, with your knowledge and the strength of your academic weight—and I say that collectively—is, you know, assist those of us here who want to move this legislation to its logical conclusion and provide—I am—I ask for your help in my colleagues' name to help us with this effort.

Dr. KIRSCHSTEIN. Dr. Collins has been doing his best.

Ms. DELAURO. I believe you.

Dr. COLLINS. Congresswoman, I really appreciate your very strong and effective statement. I should have given credit to Congresswoman Slaughter's leadership in the House in raising this issue and to the strong support she has had from you and some of

your colleagues who have made this issue much more visible than it otherwise would have been.

But you accurately state that despite all of those cosignatories, there doesn't seem to be much forward motion. I would certainly say I am willing to go anywhere at any time to make the case, backed up by fact, backed up by research, and backed up by case examples of people who have already suffered injury as a result of the lack of this kind of protection. Just point me in the right direction and I and a lot of my colleagues will be right there.

THALASSEMIA CLINICAL RESEARCH NETWORK

Ms. DELAURO. Thank you. We will take you up on your offer. Thank you very much.

Dr. Lenfant, let me ask a question, as I normally do. I have been a longtime supporter of the Cooley's Anemia Foundation and am grateful for all of the efforts in creating the Thalassemia Clinical Research Network. It is my understanding from the material that I reviewed that the network currently has two research projects that are under way, and that they are—and that you are reviewing additional projects. Can you share with the committee your assessment of the progress that has been made to date, and what steps will the institute be taking to support further research being conducted through the network?

Dr. LENFANT. Well, I would say that now we are optimistic and confident that the program is going to be successful, but I have to admit that the growing pains have been difficult. But it is working, and it is true that now they have two research projects plus one data collection project. So there are actually three activities which are going on.

I met with them last December at the American Society of Hematology, because I was very concerned that after more than 18 months of this effort, no project had actually gotten started. And I said to them, we all have a problem. Within 18 months you are going to have to consider your resubmission for the next 5 years of funding, but unless you get going, there will be nothing to show in terms of progress. And that has had some stimulating effect, and now they are moving faster, and we are confident that it will work.

I should say that the chair of the steering committee, which is the group that clearly governs the program, is a good friend of ours, a very distinguished scientist who knew what we were talking about and what the problems were, and he has done a lot to get this project going. So, Ms. DeLauro, I have to say that we can expect some very good results from these programs.

Ms. DELAURO. Thank you, and I would like to keep in touch with you on that.

Dr. LENFANT. We would be pleased to.

And I should say that in addition to that, we are supporting a number of very exciting projects of basic research which will feed into this clinical network for clinical investigations.

PREVENTING INFECTIONS IN HOSPITALS

Ms. DELAURO. Thank you.

If I might ask one more question, this is to Dr. Grady. I think one of the most challenging issues for health care in this 21st cen-

tury is the issue of infections in hospitals. My understanding is it can cost up to about $5 billion a year in terms of trying to deal with it, and that currently infections are the fifth leading cause of deaths in hospitals. They continue to be the leading cause of morbidity and mortality. Even in the United States there are over 2 million hospital infections a year, and 50 percent of patients have adverse outcomes. Yet one-third to one-half of these infections are preventable.

There are some, you know, who are suggesting that the hospital-acquired infections are this new century's, you know, most urgent health care challenge. Can you address that issue and talk about the veracity of the data, but also what is being done about it? What is the research aimed at reducing the infections of patients in hospitals?

Dr. GRADY. You have identified an age-old and persistent problem that we deal with. There are a number of infections that result within hospitals that are drug-resistant, which is a result of new technology, but the base of the problem in most cases appears to be simpler than that.

We are funding a number of studies which address the issue of hand-washing in hospital settings, how often, how effective, looking to see not only do people wash their hands, but how effective is it? Surprisingly there is a very high incidence, when you have people watching health care workers, both physicians and nurses in hospital settings, of the number who do not wash their hands at each opportunity that they should. In tracking that, the issue of using hand wash chemicals versus soap, increased friction, increased time, there are a number of techniques that are being tested out that appear to have good results. The results, in fact, are close to being published, but it is surprising when the basic principles that we have all known about are adhered to, that they actually are reasonably effective in preventing infection.

The drug-resistant infections are another case, and I know you have heard a little bit about that from my colleague Dr. Fauci, but we are funding several studies to address this, and are hopeful that we can change practice as a result.

Ms. DELAURO. Let me just ask a question about this because you said it is an age-old problem, but is this something that manifests itself and then we, you know, kind of go back to basic principles? I am not talking about the drug-resistant difficulties, but—and then it subsides and then it occurs again? I mean—.

Dr. GRADY. It would appear to be so, looking at the cycles, and how much of that is behavioral and how much of that is catching up to the newer risks and dangers in a hospital environment is a little difficult to identify. But, yes, you are right.

Ms. DELAURO. Thank you very much. Thank you.

Thank you, Mr. Chairman.

Mr. REGULA. Mr. Sherwood.

GENETICS—HEALTH PROMOTION

Mr. SHERWOOD. Thank you, Mr. Chairman.

And, Dr. Collins, even the least scientific among us can recognize that the mapping of the human genome is a tremendous accomplishment. I would like to hear your thoughts, though, on when we

will be able to use this information to cure or prevent disease. We presented very difficult choices to individuals who may be at risk for certain diseases by telling them they are at risk without telling them what we are doing about it.

Dr. COLLINS. That is a very good question, Congressman. The way in which gene discoveries occur lead one to the ability to make diagnostic predictions almost immediately after the gene discovery. But the ability to intervene, to cure the disease, takes many years. Because of the many more, difficult, and challenging steps in medical research. For instance, we already know what the major genetic risk factor is for Alzheimer's disease, yet we don't offer that test to people because we have no intervention available to those that turn out to be in the high-risk group.

There are already some valuable clinical applications though, in genetic research are moving rather rapidly, and for some diseases we already are in a circumstance where being able to identify someone at high risk can be life-saving. Colon cancer is a good example. If you are one of the roughly 1 in 400 people in a family with several affected individuals with colon cancer, and you have a gene with is a particular glitch, your intervention would be close medical surveillance and colonoscopies beginning at an early age and done very faithfully every year. That intervention has been shown to reduce morbidity and mortality by finding those polyps in the colon and getting them removed before they turn into a nasty malignancy.

One should not assume, therefore, that you have to go all the way through the steps from finding a gene to developing a drug in every case to make the information valuable. But we do want to develop the drugs and the gene therapies. And in that regard, there is a lot of excitement in the field of drug development based upon genetics. In fact that for a few diseases, we have already gone through those steps.

Take the drug Gleevec which was approved by the FDA less than 12 months ago for the treatment of leukemia. In that circumstance, the drug was specifically designed using the knowledge of the genetic glitch in those leukemia cells, and this drug specifically work to block the effect of the glitch.

There are over 100 drugs now in clinical trials, mostly for cancer, that are based on this same paradigm of understanding what the genetic problem is, designing a small molecule that will go right to the heart of the matter and block that effect. Not all of those drugs will succeed. Some of them undoubtedly will fail, but this paradigm of basing drug discovery on molecular understanding instead of a more empirical approach is already happening. Certainly every pharmaceutical company is putting their major bets on that pathway as the way to develop the drugs of the future.

So you are right. We may have to live in this uncomfortable window for some diseases between pretty good diagnostics and not so good therapeutics, but the only way to get through that is to press on. And that is what all of my colleagues at the NIH are determined to do.

NATIONAL CARDIOVASCULAR HEALTH CONFERENCE

Mr. SHERWOOD. Thank you.

I think one of the frustrations to those of us that—without the training is the length of time it sometimes takes to get the wonderful discoveries and the information that you folks have at your fingertips out to practicing medicine.

Dr. Lenfant, I understand that the National Heart, Lung and Blood Institute has just completed a very successful national cardiovascular health conference chaired by Dr. Lynn Smaha, a constituent of mine and the immediate past president of the American Heart Association—please tell us a little bit about that conference and why it was significant.

Dr. LENFANT. Well, I am very pleased that you ask this question, indeed, because that was one of the most significant events of the last few months. This conference was held last Thursday, Friday and Saturday, and the goal of the conference was to do what this hearing is about, to communicate to the practicing community as well as health care systems, health services in communities what is going on, what can be done that does not necessarily cost millions and millions, but with very little money and much effort can get the help to the patients.

The conference was attended by, I think, 1,300 physicians, nurses, health care professionals and so forth, but the interesting thing is that it was Web-cast in all of the States through the United States, and there are actually 150 contacts in all of the 50 States where people could go and watch the conference. So although we had participation here in Washington of maybe 1,200, 1,300 people, we do know that there were thousands and thousands of people out there who were in contact with what was going on, and who watched some of the best experts in the field.

And we know that we will achieve something, because we have that conference, the same one, every 3 years, and after each 3 years, we see some progress and better communication and better understanding.

And one of the things that I mentioned before you came, Mr. Sherwood, was a campaign on acting time in to heart attack signs, and the purpose of it is to educate people that they really don't have to wait to drop on the sidewalk to do something about their heart, they can do it before, and that is the kind of thing that we need to communicate to the people because it works.

OBESITY RESEARCH

Mr. SHERWOOD. Thank you very much.

I will get to the question I always ask. We find that overweight and obesity are major risk factors for many, many different diseases. Folks have been telling us that, including heart attack and stroke and other cardiovascular diseases, not to mention early onset diabetes, but the number one killer in the United States, so please tell me what the National Heart, Lung and Blood Institute is doing to address this growing problem of obesity and its tremendous effect on our health.

Dr. LENFANT. Well, we are doing a lot. In fact, we have multifaceted programs which include, of course, basic research to understand what bridges obesity and weight gain with cardiovascular disease. We have a program to fund treatments and interventions which would be successful to reduce or limit weight gain, and we

also have educational activities to really help people, especially youngsters, to prevent the development of obesity.

I believe that the scientific community is very firm on one thing. It is easier to prevent the development of weight gain than to treat it once you have it, and that is a message that we are trying to communicate through a number of programs. For example, in the conference that you mentioned earlier, there were many, many things on that very issue, what can we do to prevent obesity to develop. We have a program which is called Hearts N' Parks, which basically is working with all of the public parks in the country to develop programs so that the kids going there have physical activities, are encouraged to go there.

COMMUNITY PROGRAM

We have programs in some communities. Let me give you an interesting example. In West Virginia in one community, what we have done is to—the community has done, not us—they have painted on the sidewalk steps so that the kids there know how many steps they take each day in order to prevent the development of obesity.

ASTHMA

So we do lots of things. It is a very active part of our programs in the prevention of cardiovascular disease, and I would say respiratory disease as well. We know today that, for example, overweight children and adults are more likely to develop asthma than children who do not have an excess amount of weight.

Mr. SHERWOOD. Thank you very much.

INFORMATION AND HEALTH CARE

Mr. REGULA. Mr. Sherwood, if you didn't get these folders, be sure you—I don't know if they are in your pack there or not, but I would love to give one of these little cards to every one of my constituents. It would be so valuable to them.

Dr. Lindberg, we live in the information age. We get flooded with information, and you as chairman of that area have a lot of responsibility. You know, the question is—and this is a tough one—is the availability of all of this information that we are inundated with improving health care?

Dr. LINDBERG. Well, I agree with others who have suggested that giving the information directly to the patient is definitely the thing to do. I mean, the patients nowadays are educated and are willing to participate in health care delivery decisions and take care of themselves. So I think we can't lose by giving the information to the patients.

NLM WEBSITE

You had asked earlier about the activity on these NLM and NIH Web sites. I mean, we actually at NLM alone answer a million inquiries a day.

Mr. REGULA. A day?

Dr. LINDBERG. A day. It is a staggering amount. It has grown 400 million a year. Now, I am not sure that everybody leaves with

what they wanted when they came to that Web site, and I think that is where the opportunity lies. My own impression is that we do a very good job of providing information to health care professionals and increasingly the researchers, but that the public, I think, is looking for understanding more than they are to retrieve a piece of information. They don't really want to know the melting point of some crystal. They want to understand what is under their skin, and to just play back four-syllable Greco-Roman words may be accurate retrieval, but that doesn't give them understanding. So I think there is a lot of research to be done that in that area, and we are going about doing that.

I can give you one example of the kind of thing the public is after. In the 30 days after the terrorist use of anthrax, anthrax was searched more than everything in cancer combined, not surprisingly, but it happens that we have a very good tutorial on that and so forth. One of the things I wish I could have done in showing a poster is to show you how active it is. I mean, I was going to bring you the first speaking poster down here, but I—my technology—I didn't have time to work it out. But particularly in the older populations and low-vision populations, there is no point filling a screen up with thousands and thousands of little characters. Nobody can read them. In fact, I don't like reading them either. So increasingly we are having them read themselves, to say the words, and to show some television. So, for instance, part of it is understanding; part of it is attitude. Dr. Lenfant, we work with him happily on the collaborative Heart Attack Alert program. We know it is often an attitude of delaying that stops people from getting help they need.

Now, this same thing is behind everybody's worry about Alzheimer's, and we are working with the Aging Institute to produce a senior health page, and it has a lot of good attributes, but the thing that appeals to me most strongly about it is that it can show you a television interview, a psychiatrist interviewing a patient, do you have Alzheimer's. And actually there are two, one that does, one that doesn't, but in most cases a member of the public would leave that interview relieved. I mean, they would say, well, okay, I am not like that. I don't have to worry about that. It is tremendously relieving to improve the attitude toward that disease to see this kind of a little thing, and we are working very hard to make sure that technically it will, you know, download fast enough on an ordinary phone line and that sort of thing. We don't want to put it up if it is only of use to you in great medical centers. We want it to be able to get out to where the people are.

Mr. REGULA. About a year or so ago, we had a meningitis scare in my area, and, of course, parents particularly were very alarmed. Now, could they have plugged into your Web site, put in the key word "meningitis" and gained information that would have given some degree of assurance to them or some ideas of how they should react to this scare that was travelling through the community, schools closed, et cetera?

Dr. LINDBERG. Oh, absolutely. This 570 health care topics, though I can't swear to you absolutely that meningitis is there, but——

Mr. REGULA. No. I am just using that as an analogy.

Dr. LINDBERG. I am sure that it is. The challenge there—we are actually actively pursuing with grants in a lot of States. The problem is how to localize the knowledge. In other words, I am certain that we tell you what meningitis is and so forth, but then the person immediately wants to know, well, where do I go? I mean, where is the local place to get tested or get immunized or get weighed or blood pressure, and that is really a very difficult proposition.

LOCALIZE INFORMATION ON THE NUM WEBSITE

Mr. REGULA. But you could tell them that they could get immunized or suggest it on the Web site?

Dr. LINDBERG. I can, and no doubt we do, but I can't tell them that if you go down to the——

Mr. REGULA. Right.

Dr. LINDBERG [continuing]. Corner of 4th and Main, there is a public health place.

Mr. REGULA. No. I understand.

Dr. LINDBERG. And that is what we would like to be able to do. Years ago we were testing the system of how to work in public libraries, because not all—about half of the people have computers, and I think we do pretty well by them. The other half don't, so public libraries is one of the places we are doing the experiment, and one of those was New York Public.

And I went there, and it was a very successful experiment, but just to test them out, I said something about flu, and it immediately was smart enough to understand about—I really meant influenza, and it was an infectious disease, and you could immunize—and so I said to them, okay, where do I go? This was at 57th Street and 5th Avenue, and it said Albany, because it went out and did a big Web search. I mean, it was right, but it didn't localize it for us. So that is the problem we are working on right now.

Mr. REGULA. But nevertheless, if someone went to the doctor and received a diagnosis that said you have a melanoma, that person could go to the library or go home and plug in melanoma and get, I would assume, a wealth of information?

Dr. LINDBERG. Yes, yes. They would get the right information, and I think that is a good example, because if you are sitting in the doctor's office, and he says that terrible word to you, that is not a good learning opportunity. I mean, you want to go back and, you know, crawl under the covers and emerge when you have got enough equanimity to study it. That is exactly what it is all about.

Dr. KIRSCHSTEIN. Dr. Lindberg might like to tell you about the clinicaltrials.gov.

CLINICAL TRIALS

Dr. LINDBERG. Clinicaltrials.gov is going very, very well. I mean, that, as I said, is something that was called for in the legislation reforming FDA, modernizing FDA. But Dr. Varmus asked NLM to initiate that at NIH, and so all of the trials—the first step was to put in the trials supported by NIH, which is now some 5,700. There are also now are some supported in the AIDS area by other associations, and now we are starting to work with the drug companies,

but that has a very brisk utilization. It is designed for the public. That was the Congress's intent.

It actually is tremendously useful to the doctors. In fact, a number of the NIH institute directors have told me that that is the first place they go to answer a lot of different questions, and it gets around the problem that—I mean, it is nice, though, we have the institutes, and they are a lot more self-explanatory than CDC, but on the other hand, we don't want to expect that the patient has to understand how we are organized, how their own organs are organized and then how the agencies are organized. I mean, this cancer research is supported in clinical trials in cancer in virtually all of the institutes. It isn't all NCI. So it serves a very good purpose to have—I mean, I salute the Congress once again. You have led the way in bringing common sense to these biomedical problems.

CONSOLIDATION OF PUBLIC AFFAIRS FUNCTIONS

Mr. REGULA. Dr. Kirschstein, what impact do you think the Secretary—Secretary Thompson's initiative to consolidate all agency public affairs functions—and we have been talking a lot here about the information—will have on NIH's routine dissemination of scientific information? In other words, I assume—well, you are aware of the efforts he is making.

Dr. KIRSCHSTEIN. Mr. Regula, NIH is not in the business of running offices of public affairs. We are in the business and providing scientific and health information to the American public, and we have presented to the Secretary, and he basically agrees, that that information is best provided by having the people who know how to write scientific material that, is understood by the public, work closely and in conjunction with the scientists within the particular institutes involved, the directors, their programs and even the researchers at the bench. And therefore, we have agreed that when there is to be a public announcement, a press release or something of the sort, we will do what we always have done, which is to work with the Secretary's Office of Public Affairs to make sure that the message that the Department wishes to put out there is correct. But for the vast amount of material that we handle, we will be allowed at the local source, meaning the institutes, the centers, the Office of the Director, to do this in conjunction with the scientists.

Mr. REGULA. Speaking of information, I think it would be useful, because—through the medium of television a lot of people will have the opportunity to hear this testimony, and that is great. I wonder if you might describe briefly the procedure. Mr. Obey mentioned that you maybe do 30 percent of the requests or grants. I am not sure that most people understand. I would suspect if you were to ask a lot of people, they would assume that you were doing the research out at the NIH campus, and I think it would be interesting for people to recognize or to understand the vast array of resources you bring to bear on this, which essentially is the entire academic community of America. But just procedurally how does it work?

Dr. KIRSCHSTEIN. Mr. Chairman, the appropriation that you provide to NIH, Congress and the President every year, is divided in essentially two parts. One part of that is about 80 percent, 85 percent of the budget, which is expended for doing research, research training, various activities related to research, science communica-

tion at the great medical and academic institutions throughout the country of the United States, across the entire horizon of the country, as well as to small business organizations and to research institutions which have academic backgrounds, but not necessarily affiliated with academic institutions.

INTRAMURAL RESEARCH

A very small percent, 10 percent, is expended in research that is carried out in what is called the intramural program of the National Institutes of Health collectively. That is divided up between all of my colleagues——

Mr. REGULA. And this would be led by these gentlemen and ladies?

Dr. KIRSCHSTEIN. Well, these gentlemen have the responsibility of leading both programs in terms of where the science should be moving—gentlemen and ladies, I might say—programs as to where the science is moving and to how best to expend those funds, but basically it is to determine what is important. However, what we call the intramural program, the scientists who work for each of the institutes at NIH, the vast majority of them are within the Bethesda campus. But Dr. Olden's campus is, for example, in North Carolina where he has that responsibility.

They have that responsibility, too. They have the responsibility for weighing the balance between those two efforts. It is not by accident that approximately 10 percent is spent within the intramural programs. It is not by accident that coincident with the growth of our great academic institutions in the United States, doing biomedical research starting at the end of World War II, has made the United States the premiere country in the world and it is because that balance of about 85 percent, 10 percent and a small amount to make sure that the lights and the heat and so forth are provided, that we get the most research effort and the best scientists working in the United States so that scientists from all across the world come to those institutions, as well as to the NIH itself, to learn and work with our prestigious scientists.

Mr. REGULA. Well, I am struck when I run into the—or have a conversation with the heads of some of our major universities in Ohio, and I will say to them, do you have NIH grants, and they say oh, yes, we have several. So obviously you are using the resources of the Nation to do these studies on various areas. And each of these people who have participated today and in previous hearings would have responsibility for the field that they lead, and procedurally my institution has—through the medical research, thinks they have a good idea in finding a cure for Alzheimer's. Procedurally what would we do?

GRANTS APPLICATION PROCESS

Dr. KIRSCHSTEIN. They have the good idea. They would prepare what is called a research grant application. The institution would help the individual scientist to put it in a form that is needed, and it is submitted to the National Institutes of Health.

Two decisions then have to be made. One is as to which of these various institutes that research grant application would be assigned. If it is Alzheimer's in general, it would be assigned to the

National Institute on Aging. However, it is possible if it stresses the behavioral aspects of Alzheimer's disease that it would be assigned to the National Institute of Mental Health, and if it stressed some of the neurological aspects, the National Institute of Neurological Diseases and Strokes, so that you can see that may be more than one institute. And indeed some grant applications are assigned to more than one institute to give the grantee, the applicant out there in academia, the opportunity to receive funding independent on the budgets of each of these——

Mr. REGULA. So it could be for more than just one of your institutes?

Dr. KIRSCHSTEIN. Yes.

The second thing that happens, the second place it is assigned is to what we call the study section. You heard a description of that from Dr. Ehrerfeld about 2 or 3 weeks ago now, in which we assemble a group of, again, scientists from academic institutions with expertise, broad-ranging expertise, in the area of neurological diseases, problems of aging, mental health, et cetera, in heart disease, if it is a grant application related to heart, who do a review of that grant application in concert with a large number of others, sometimes as many as 100 at a meeting which lasts 3 days and is very often held 3 times a year. That is a peer review.

So the scientist at the academic institution that originally submitted the grant application receives the views, scientifically based, of his or her colleagues. That leads to an assessment of the scientific merit of that grant application, and finally to the second level of review, which Congress in its wisdom set up, which is the advisory council mechanism, where not only do the senior scientists in the field, but the public, the public that knows something about heart disease, knows something about the ethical issues related to genome, about dental caries in the United States, about nursing, et cetera, et cetera, weighs in on what is the relevance of that particular grant application to the improvement of the health through either diagnosis, prevention, possibly cure and sometimes treatment of that disease or that entity, and those two reviews together lead to the decisions dependent on the funds that each of the institutes has as to whether that grant application gets funded or not.

Anybody want to add anything?

Mr. REGULA. So what percent of the applications you receive—was there some kind of a benchmark? Is it 100 percent of them or 75 or 20?

Dr. KIRSCHSTEIN. We have had submission of grant applications of such remarkable scientific merit that we are funding, with the excellent budget that the Congress has given us over the last 5 years, about one-third, 30 percent, of those that are received. I think most of my colleagues feel that at this point in time the excellence of the next group, 5 percent, 10 percent, is sufficient to be able to continue to fund if there were money and in addition there was relevance; that we would not be ashamed, but we would be proud to provide those funds.

Mr. REGULA. So you are saying most all of it that are submitted are high quality, so you are choosing between quality and quality plus.

Dr. KIRSCHSTEIN. That is right. And part of that is also a very important task that we have all done for many years, and that is training young people to become medical and scientific biomedical researchers. They are the seed corn by which we provide the American public the assurance that in the future this will continue on.

LIFE EXPECTANCY

Mr. REGULA. What has happened in life expectancy in the last 10 years, because obviously the work you do can contribute greatly to that?

Dr. KIRSCHSTEIN. A great jump happened somewhat more than 10 years ago, but each year is continuing apace. Now, in his—yes, please.

Dr. LENFANT. That is an issue that we went over very carefully. Each 5 years during the last 30 years, life expectancy has increased by 1 year, so during the last 30 years, 6 years. Sixty percent of that gain in life expectancy is due to the decline in death rate of cardiovascular disease. So that really is a tribute to the research establishment and to the Congress who have supported this.

I can tell you that if that did not happen, instead of 500,000 deaths from cardiovascular disease that I mentioned at the beginning, we would have in this country 1.8 million deaths each year of cardiovascular disease.

Mr. REGULA. I assume the quality of life, in addition to living longer, you live better as a result of all of this research.

Dr. KIRSCHSTEIN. In general, that is true. However, that is of concern, because if the quality of life is not really better, there is some question about it. And the more we can do to turn what were acute diseases, heart attack, into a chronic situation, the more we have to be careful about making sure that the quality of life remains at a level that makes people useful, productive citizens, even into their retirement years.

Mr. REGULA. Interesting.

Mr. Sherwood, any——

ASTHMA

Mr. SHERWOOD. Thank you.

Dr. Olden, I understand that the National Institute of Environmental Health Sciences has been pursuing research into the connection between asthma and indoor pollutants such as dust mites and other things, and I am wondering if any studies have been done on the amount of time children spend inside and any correlating increase in rates of asthma.

Dr. OLDEN. Yes, Mr. Sherwood, that kind of research has been done. But let me say it has been done in collaboration with two other Institutes. Dr. Lenfant's Institute, the National Heart, Lung and Blood Institute, and the National Institute of Allergy and Infectious Diseases. And so maybe Dr. Lenfant would also like to comment.

But yes, we, in partnership with HUD, conducted a national allergen survey—a population-based survey of selected regions throughout the United States. We identified a number of allergens—certainly the allergens that are responsible mostly for asthma are dust mite allergens, cockroach allergens, and indoor ciga-

rette smoking. And yes, studies do demonstrate that kids today spend much more time indoors than kids a few years ago, and the synthetic chemicals and off-gassing of materials that are used in building houses is also a problem that certainly exacerbates the asthmatic conditions in people who are genetically predisposed to have the disease.

Mr. SHERWOOD. It occurs to me that the advances we make in society to make our lives easier, with the exception of workplace injuries and obvious things like that, also make our job a little harder to protect our good health, and that a television set is no substitute for a baseball for a healthy kid.

Dr. OLDEN. That is right—television, computers. Construction is much tighter. When we were kids and air could come through the cracks in the house, we thought that was a disadvantage, but it turns out that it is an advantage.

There are a number of issues. Mold growing in homes is also a major problem that certainly exacerbates asthma and other pulmonary dysfunctions. But there is a lot of research going on in three institutes in the NIH.

Mr. SHERWOOD. So in our homes in the Northeast a few years ago, it was all the rage to make them very tight so they would be more energy-efficient. And you still need your air flow or your air exchange, and energy efficiency and good health might necessarily—might work at cross purposes here.

Dr. OLDEN. That is correct. Also building and construction materials contain a lot of synthetics, and they off-gas over the years, and certainly that creates a lot of respiratory discomforts and problems.

Mr. SHERWOOD. Thank you.

Mr. Chairman, it is wonderful the knowledge that we have at our disposal here around this big table. It is a rare treat. Thank you very much, folks.

Mr. REGULA. The big challenge is to use it effectively, yes.

Last question, will the routine dissemination of scientific information, which all of you do with your Web sites, be carried out at the department level or at NIH?

Dr. KIRSCHSTEIN. At NIH.

Mr. REGULA. At NIH. So there is no change in that?

Dr. KIRSCHSTEIN. That is our understanding.

Mr. REGULA. Well, my thanks to all of you, and I think this has been a very valuable hearing both for us and for those that have an opportunity to view it out in TV-land because health is important to everyone and of course the quality of life is so much affected by having good health, and I think the American public is indebted to all of you for providing leadership in these research fields to achieve those goals and I am sure that plugging into your Web site is a comfort to people oftentimes because the medical profession doesn't always have the time to spend an hour with a patient saying these are all the elements of the diagnosis you have received and your Web site would be very useful in that respect. And I suppose you've get hits from people who got an ache or a pain of some kind and are just at home and it is on Sunday and they say, well, I would like to know what this is all about and they can use your

Web site instead of these medical books that are sitting on our shelves.

So, Dr. Kirschstein, we wish you well, and whatever challenge you have——

Dr. KIRSCHSTEIN. Thank you and the other members for giving us these opportunities over the last number of weeks and several months to present to you.

Mr. REGULA. I think the persuasiveness of your testimony will probably be reflected in our budget numbers. At least that is the goal. Thank you all for coming. The hearing is adjourned.

ENHANCED DISSEMINATION AND UTILIZATION CENTERS

Mr. Regula: NHLBI has funded several Centers to conduct performance-based education projects. Describe these projects in further detail.

Dr. Lenfant: In March 2001, six community-based Cardiovascular Disease (CVD) Enhanced Dissemination and Utilization Centers (EDUCs) were funded to conduct performance-based projects to eliminate health disparities (racial, ethnic, and geographic disparities) as part of the Institute's response to the Healthy People 2010 objectives for the nation. Serving high-risk populations in over 21 U.S. counties, the EDUCs are intended to form the cornerstone of a nationwide network of performance partners that will use the Institute's science-based health education materials to inform their communities of the public health burden of CVD, and to develop, implement, and evaluate focused educational strategies for their populations to improve their cardiovascular health status. The NHLBI plans to fund an additional eight EDUCs in FY 2002.

The EDUCs employ multiple approaches to reach a wide variety of populations. For example, the Danville, Virginia, project, which targets low-income, underserved African Americans and whites, is using community-wide risk factor screenings and referrals, school-based screenings and health education and physical activity programs, and continuing medical education for physicians regarding national guidelines on cholesterol, blood pressure, and overweight and obesity. The EDUC in the Mississippi Delta Region of Arkansas is implementing professional education and church-based health education programs to improve cardiovascular health in two rural counties that suffer from extreme poverty and low educational attainment rates. In Huntington, West Virginia, St. Mary's Hospital, in collaboration with the State Education and Health Departments and the local American Heart Association chapter, is implementing a school-based intervention for 8,000 students in grades 3-5, their families, and school staff in 45 Appalachian public schools. The community is medically underserved and has high rates of unemployment, poverty, poor health, and geographic isolation, and low education levels. In the Ft. Worth-Metroplex area of Texas, the University of North Texas Health Science Center is developing a comprehensive health promotion, health education, and outreach initiative to increase awareness and knowledge about CVD prevention and promote heart healthy lifestyles among Hispanics. The project is using materials and tools developed by the NHLBI to train lay health educators or "promotores" to help identify individuals with CVD risk factors and guide them through treatment and followup. In Robeson and Columbus Counties, North Carolina, the Wake Forest University School of Medicine EDUC is working to improve health care services to Native American and African Americans. The project is providing training for primary care physicians and health clinics on the use of low-cost strategies for treating individuals with high blood pressure and high blood cholesterol, and is also working with local community-based organizations to help them improve their advocacy efforts for environmental policy changes to promote heart health. West Virginia Health Right, Inc., a free clinic in Charleston, West Virginia, which serves the uninsured and

underinsured in the poor south-central part of the state, is evaluating intensive behavioral interventions in physical activity, nutrition, weight loss, and smoking cessation in addition to best medical practices, including pharmacological, diagnostic, and therapeutic interventions.

DEVELOPMENT OF EDUCATIONAL MATERIALS

Mr. Regula: In addition to the racial and ethnic disparities that exist in health, research is also finding that there is a gender and ethnic difference in the effectiveness of some treatments. What problem does this pose in the development of educational materials for dissemination?

Dr. Lenfant: It is true that the research we have supported has produced some notable findings of differences in effectiveness of treatments based on both gender and ethnicity. We know, for example, that blacks with hypertension are less responsive than their white counterparts to treatments with either ACE inhibitors or beta-blockers alone. This is an important finding and one that should have a major impact on how physicians treat their patients and it has already been incorporated into the recommendations of the National High Blood Pressure Education Program regarding treatment of high blood pressure.

However, most of our messages for patients and the general public will be unaffected by such results; they will remain valid for all Americans irrespective of any findings regarding differential responses to treatment. For example, our National High Blood Pressure Education Program will continue to urge people to get their blood pressure checked, to see their physician if it is elevated, to take their blood pressure medication if any is prescribed, to exercise regularly, to reduce their use of salt and eat a healthful diet, to stop smoking if they smoke, to lose weight if they are overweight, and to limit their consumption of alcohol. The same may be said for our National Cholesterol Education Program and our National Asthma Education and Prevention Program. As for the National Heart Attack Alert Program, its primary message for the public is "Act in Time to Heart Attack Signs," a message that has nothing to do with how a heart attack is treated, but everything to do with getting patients to seek treatment immediately upon the onset of symptoms. We will certainly continue to monitor the research developments relating to differences in response to treatment and make appropriate adjustments to our messages as needed, but for the foreseeable future I feel confident that the recommendations included in our educational materials will remain valid for all Americans.

PROGRESS OF TASK FORCE ON COLLEGE DRINKING

Mr. Regula: The Subcommittee on College Drinking, a collaboration between researchers and college presidents, has been meeting since 1998. What progress has this collaboration made in preventing drinking by students?

Dr. Kington: On April 9, the Task Force on College Drinking issued its findings in formats that have practical applications for different audiences. The Task Force's report includes recommendations for both the college and research communities, and we are sending this report to all 3,600 college and university presidents in the Nation. Nineteen papers commissioned by the Task Force have been published in peer-reviewed journals for the research community. Administrators will receive a primer on how to evaluate their schools' prevention programs. College presidents, parents, and peer educators now have access to three brochures relevant to each of them. An interactive website is providing all of these audiences and the general public with information about college drinking and approaches to preventing it.

This Fall, NIAAA will begin to sponsor a number of regional workshops, across the country, for college presidents, deans of student affairs, and student-health providers, to discuss the Task Force and its recommendations. Implementation of the research recommendations have already begun; for example, the Multi-Campus Comprehensive Prevention Study is underway at 16 campuses of the two California university systems.

PROGRESS OF TASK FORCE ON COLLEGE DRINKING

Mr. Regula: Has student drinking on college campuses been reduced?

Dr. Kington: The recently released Task Force report cited disturbing new data on college students between the ages of 18 and 24. Each year, about 1,400 of them die of unintentional alcohol-related injuries; more than 600,000 students are assaulted by other students who have been drinking; 400,000 students who have been drinking have unprotected sex; and more than 70,000 students are victims of alcohol-related sexual assault or date rape. Other data collected over the past 10 years suggest that the number of abstainers on campus is increasing and that the number of students who binge drink remains constant or has decreased slightly. The consequences generated by those who do drink are very destructive and extend far beyond the harm they cause to themselves.

The Task Force is a first step in changing the culture of campuses and their surrounding communities in ways that reduce the consequences of drinking. Of the Task Force's many recommendations to college presidents and researchers, the most critical is to routinely collect better data on college drinking and its consequences, to enable them to measure the effectiveness of preventive interventions.

COLLABORATIONS BETWEEN NIAAA AND SAMHSA

Mr. Regula: NIAAA intends to expand collaborations with SAMHSA in fiscal year 2003 to enable a more rapid translation of research findings into the delivery of services. How do you propose to do this? What will you do differently? Will NIAAA and SAMHSA also develop performance measures?

Dr. Kington: NIAAA and SAMHSA have contacted one another regarding expansion of their collaborative efforts, and will meet on a regular basis regarding this issue. This increased collaboration is critical to shorten the time period between advanced research and improvements in the delivery of services. Currently, NIAAA activities to which SAMHSA contributes include National Alcohol Screening Day, the Leadership to Keep Children Alcohol Free, and prevention of underage drinking. The two agencies also collaborate on the Researcher-in-Residence Program, and SAMHSA is represented on the NIAAA-chaired Interagency Coordinating Committee on Fetal Alcohol Syndrome.

The Substance Abuse and Mental Health Services Administration has a pool of researchers, some of whom could contribute to NIAAA's research mission, especially in the health services area. NIAAA has obtained SAMHSA's mailing key and will use it to invite applications from SAMHSA's grantees. Highly qualified applicants will have the potential for being awarded grants.

SAMHSA, NIAAA, NIDA, and NIMH leadership have begun meeting regularly to discuss further collaborations and issues related to our common missions. We consider development of performance measures one of the important issues that require further discussion.

NEIBank

Mr. Regula: NEI recently established a website called NEIBank. Tell me more about this website. If I were to use it, what kind of information would it contain that would be useful to me?

Dr. Sieving: The NEIBank website was first released on July 8, 2001 and serves as a global resource for vision researchers who are gathering information on genes that are expressed in the eye. The site is designed for the sharing of data and the facilitation of research and communication on vision and eye disease. At present, the NEIBank contains four categories of resources. The first is cDNA gene sequences from a variety of libraries that are grouped according to nine eye tissue types. cDNA libraries serve as a central resource for discovering new genes and allow the study of tissue-specific gene expression. For example, if researchers wanted to know a specific gene sequence for cornea tissue, they would select the CORNEA link that would direct them to a library of full-length cDNA sequences where they could search for the particular sequence of interest. The three other resource categories are the NEIBank-L, which is an electronic mail list to alert the research community when new features are added; links of interest to other biotechnology, bioinformatics, ocular genetics, and other ocular anatomy websites; and ocular gene sequence resources. The NEIBank is continuously updated using input from a steering committee of scientists from the vision research community.

Although the NEIBank was primarily designed to aid vision researchers, citizens who suffer from eye disease will indirectly reap the benefits of its existence. The identification of genes expressed in the visual system increases the potential for creating novel, gene-based therapies and treatments for people suffering from eye diseases such as retinitis pigmentosa, age-related macular degeneration (AMD), and glaucoma. The NEIBank can be accessed via the Internet at (http://neibank.nei.nih.gov).

INTRAMURAL RESEARCH AT NINR

Mr. Regula: NINR's intramural research program is increasing its focus on health promotion and symptom management. Tell me more about this. What do you hope to accomplish?

Dr. Grady: Within the 21st century, health promotion and symptom management will be key to a healthier nation. The NINR Division of Intramural Research (DIR) focuses on research and training in these areas. NINR is building its intramural research program through its Symptom Management and Health Promotion Laboratories. The symptom management lab is designed to study patients' symptoms that interfere with quality of life and patients' ability to follow a treatment regimen. The results of studies from this laboratory will help patients better manage their own symptoms which may accompany many chronic illnesses and conditions.

The Health Promotion Laboratory will study the science of promoting health among individuals across the lifespan. This will be accomplished by focusing on reducing risky behaviors, as well as by improving healthy habits of nutrition, diet, and rest/relaxation. The purpose of advancing the science of health promotion is to reduce the effects of disease and disability.

HEALTH PROMOTION FOR ADOLESCENTS

Mr. Regula: NINR conducts research that supports the care of individuals across the life span. Since changing health behaviors at an early age has such an impact later in life, give me some examples of health promotion research you are conducting in adolescents.

Dr. Grady: We fund a number of studies in this area, including one in the stroke belt State of North Carolina to prevent obesity, cardiovascular disease (CVD) and diabetes in children and adolescents. Following initial results that showed elementary school children's risk for CVD was reduced in just eight weeks by a special school health and physical activity program, investigators duplicated the intervention in middle school students, with similar results. Both study populations, 4,000 young people aged 8 to 18, are being evaluated annually for CVD risk factors, such as high cholesterol, increased body mass, and high blood pressure.

In a subset of 700 healthy children, 7 percent had three leading risk factors for CVD, including type II diabetes. Researchers indicate the significant factor to predict which children are at risk for diabetes is obesity. These children are likely to develop type II diabetes within 10 years.

This research continues to provide insights for school-based health promotion interventions for young people. The North Carolina school system hopes to expand the intervention throughout the State educational system.

Another important group is that of young people with type 1 diabetes. NINR researchers conducted a study in which coping skills training added to the standard therapy of young adolescents with diabetes helped them better control their disorder. The 6-week training involved social problem-solving, communication and social skills, cognitive behavior modification, and conflict resolution. At the one-year follow-up, participants who received coping skills training maintained a drop of 1.6 points in their hemoglobin Alc levels, compared to a .7 drop in controls. In addition to better metabolic control, these teens also showed reduced depression and maintained their self confidence that they could continue to manage their disease. Over 200 practitioners have incorporated the training program as part of their routine care of adolescents with diabetes.

Other research focuses on a leading cause of death among teenagers – suicide. The few tested prevention programs available are applied to people of college age, not to younger people. Nurse researchers studied three suicide prevention interventions for 460 urban high school students from seven Pacific Northwest schools. Findings show all three interventions improved suicide risk behaviors (such as poor performance in school, family strains), anger management, and coping with family members. These initial findings indicate that suicide intervention programs based in the school can work for high school students.

NHGRI MENTORSHIP NETWORK

Mr. Regula: NHGRI has developed a mentorship network program. Describe this program in further detail.

Dr. Collins: The National Human Genome Research Institute (NHGRI) has sponsored an exciting new multimedia educational kit, "The Human Genome Project: Exploring Our Molecular Selves" to help improve life sciences education in the nation's schools by ensuring that science teachers throughout the country have better access to the latest information about the Human Genome Project (HGP), genomics, and genetics.

As an additional resource, NHGRI has developed a mentorship network program to help local high school classrooms effectively use the education kit. Members of the scientific community, including members of the American Society of Human Genetics (ASHG) were recruited to participate in an HGP/ASHG mentorship network program. To date, over 600 volunteers have signed onto the program.

NHGRI recently launched a web version of the education kit available in two formats, download modules and online viewing. As of May 2002, the mentorship program will also be accessible online through a database that will allow users to search for mentors both nationally (by state) and internationally (by country). Teachers will be able to access detailed information and contact mentors to: 1) ask questions to clarify the underlying science in the materials; 2) increase their comfort level in teaching and incorporating use of the kit into their lesson plans; 3) invite mentors to speak in their classrooms; or 4) inquire about bringing their classes to a mentor's lab/clinic to learn first hand what they do. To ensure the use of both the mentorship program and the online kit, NHGRI plans to publicize the availability of these resources in the National Association of Biology Teachers (NABT) and the National Science Teachers Association (NSTA) newsletters and similar publications.

GENETIC AND RARE DISEASES INFORMATION CENTER

Mr. Regula: Tell me about the Genetic and Rare Diseases Information Center that NHGRI has established with the Office of Rare Diseases. How is this Center going to help those suffering from a rare disease and their families?

Dr. Collins: The Genetic and Rare Diseases Information Center was established to facilitate and enhance knowledge and understanding of genetic and rare disorders through the effective dissemination of information. The purpose of the Center is to: 1) serve as a central source of information materials and resources on genetic and rare diseases, conditions, and disorders; 2) collect, produce, update, and disseminate information on the diagnosis, treatment, prevention, and research of genetic and rare disorders; and 3) coordinate with organizations and associations interested in genetic and rare disorders to explore networking capabilities, avoid duplication of effort and identify information gaps.

The Center focuses on meeting the information needs of requesters, including patients and their families, health care professionals, and biomedical researchers by carrying out the following main activities:

- Compilation and electronic storage of materials on genetic and rare diseases and disorders
- Ongoing operation of an information service with toll-free telephone service and capacity to respond to inquiries received through e-mail, facsimile, and U.S. mail
- Development and distribution of informational materials
- Collaboration and coordination with professional organizations and voluntary patient support organizations concerned with genetic and rare disorders, conditions, and diseases

- Outreach to identify potential users of the Center and provide information about the services of the Center to the intended audience.

Telephone calls to the Center are answered Monday through Friday, from 12 p.m. to 6 p.m. Eastern Time by both telephone and TTY. Inquiries can also be sent to the Center via e-mail, facsimile, or by U.S. mail.

The Center delivers free and immediate access to specialists who provide accurate, reliable information about genetic and rare diseases to patients and their families. The Center provides callers with authoritative information about specific illnesses from existing public domain sources, including reliable websites, brochures, and articles. Specialists at the Center ensure that the information sent out is current, accurate, prompt, and sensitive.

PREVENTION STRATEGIES

Mr. Regula: Environmental factors play a significant role in the onset of most chronic diseases. What prevention strategies has NIEHS developed and how is this information disseminated?

Dr. Olden: NIEHS supports much of the research that establishes the environmental components of diseases and disorders. Many of these discoveries – such as the health effects of air pollution, lead, and mercury – recommend prevention strategies that operate via regulatory and legislative actions. Other discoveries – such as simple ways to reduce household allergen exposures in order to reduce asthma attacks – recommend prevention strategies that operate at the community level. Thus NIEHS relies on a number of different venues to effect change.

There are a number of standard practices that NIEHS engages in to disseminate information. These include publication of study results, press releases of significant findings, a web site, and brochures and pamphlets on prevention strategies that are given to schools, distributed at town meetings, and made available at various conferences throughout the country. The Institute also has a journal, Environmental Health Perspectives, that serves as a unified forum for publication of significant results, as well as news articles on environmental issues of importance. The NIEHS also has close contact with regulatory agencies so that they are informed of critical data as it becomes available. There is a mechanism that allows for early release of information to regulatory agencies if an ongoing study of the National Toxicology Program (NTP) reveals serious health risks.

These mechanisms are augmented by other, more novel, approaches. The NTP Report on Carcinogens, which catalogs and evaluates data on all known carcinogens, is updated and published regularly. It has been of great value in empowering community groups and state environmental agencies to initiate prevention strategies. The NTP is also redesigning its web site so that all study data can be accessible to the public,

including a statistical package that would enable individuals to evaluate study results for themselves. The NIEHS has also established a number of Centers throughout the country and has made it a requirement that each Center have a Community Outreach and Education Program (COEP). Each program is tailored to address environmental needs of its particular area, especially of disadvantaged populations. The NIEHS also developed Environmental Justice and Community-Based Participatory Research grants that enable community groups to partner with academic organizations to design and implement prevention strategies that target diseases or conditions, such as asthma or lead exposure, of particular importance to disadvantaged populations.

STUDIES RELATED TO TERRORISTS' ATTACKS

Mr. Regula: NIEHS has initiated a number of studies related to the terrorists' attacks of September 11, 2001. Tell me more about what you are doing in this area.

Dr. Olden: Shortly after the September 11 attack on the World Trade Center (WTC), NIEHS provided supplemental funds to each of five Environmental Health Sciences Core Centers, Columbia University, New York University (NYU), Mount Sinai, University of Medicine and Dentistry of New Jersey and Johns Hopkins University. With these funds, the five Centers began collecting indoor and outdoor air samples, as well as dust samples, and initiated sample analysis; began identifying workers at the WTC for health assessments; coordinated community meetings, and initiated the development of a coordinated research agenda in three areas critically important for understanding the potential short and long term health effects resulting from this unprecedented attack --exposure assessment, epidemiology, and community outreach and education. As part of the federal response to September 11, NIEHS received 2001 Emergency Supplemental Appropriations Act funds to support WTC response activities specifically related to research in these three areas. Six awards were made in April 2002 to Columbia University, New York University, Mount Sinai, University of Medicine and Dentistry of New Jersey, Johns Hopkins University and the University of North Carolina in Chapel Hill.

The funds awarded to the six grantees will support important WTC research. In exposure assessment, a relational database will be developed for WTC-related air monitoring data compiled from NIEHS-supported research. Chemical and elemental analysis of air and dust samples from both indoor and outdoor sources will be continued at several of the universities. Personal monitoring data will be collected and analyzed. An analysis of soils and sediments in New York harbor and urban park lakes to reconstruct chemical and elemental depositional fluxes following 9/11 will be initiated. Several modeling approaches including spatio-temporal mapping and new computational models are being developed that will aid in predicting the effects of the WTC collapse on air quality, and that can be used in the future to predict the impact of such events on air quality and microenvironments.

Several projects are being initiated in the area of clinical studies and epidemiology. The NIEHS grantees are developing a registry of WTC site clean-up workers that is anticipated to include 3,000 to 4,000 workers. Respiratory symptoms and psychological health assessments are being conducted on these workers. A clinical and epidemiology study of 200 WTC ironworkers will focus on respiratory abnormalities and post-traumatic stress symptoms and in a WTC-New York City (NYC) firefighters clinical study 300 firefighters will be assessed for cardio-pulmonary effects. The NYC firefighters study is being done in collaboration with Center for Disease Control (CDC), National Institute of Occupational Safety and Health (NIOSH), the Bureau of Health Services of the Fire Department of New York (FDNY) and NYU. In addition, to these clinical/epidemiology projects focused on WTC workers, several studies focus on the general population. There are two epidemiological studies of women pregnant at the time of the WTC attacks. These studies will assess pregnancy outcome and the relationships of the WTC to child development. A third pregnancy study will look at reproductive outcome utilizing existing databases of all births recorded in New Jersey, the five boroughs of NYC, and the six closest counties to NYC to assess gender ratio, premature birth and birth defects following September 11. A WTC resident respiratory impact study is being supported to examine the prevalence of respiratory symptoms. Questionnaires will be sent to over 6000 residents. A study of residents will focus on integrating exposure data with an analysis of psychological symptoms of post-traumatic stress, depression and panic.

An important component of our research agenda focused on the WTC is the need to keep the public informed of the results and proposed actions that should be taken to minimize potential toxic exposures, as well as hearing from the public regarding its concerns. Community outreach activities include the development of a "short course" to enable the public to understand and interpret air monitoring data included in the database being developed. Focus group meetings for workers and the general population will be held to identify concerns, and the development of different approaches to disseminate WTC information includes the use of the web, public meetings, newsletters and video development.

HEALTHY PEOPLE 2010 ELECTRONIC GATEWAY

Mr. Regula: Describe the Healthy People 2010 Electronic Gateway project in further detail.

Dr. Lenfant: To create an optimal intersection of people, health information, and technology, the NHLBI developed and launched its Web-based Health Information Network and associated Healthy People (HP) 2010 Gateway just over 2 years ago. The Gateway reflects the Institute's commitment to national health goals and objectives of the Department of Health and Human Services, enables visitors to view the Institute's current HP 2010 performance projects and partners, encourages them to use the information and resources that are being generated by the NHLBI performance teams, and provides an opportunity to complete an electronic application to become a Network partner.

Network partners receive electronic notification of new NHLBI educational products and services available online including new educational products, late-breaking news of NHLBI-funded research findings, notification of NHLBI Webcasts of meetings and conferences, distance learning opportunities, and special WEB site applications such as interactive disease mortality maps to assess the magnitude of the public health burden of disease by state and Health Service Area, and new applications for the increasingly popular personal digital assistants or hand-held computers. Network membership is increasing daily; it currently numbers nearly 32,000 and includes health care providers and public health practitioners from all 50 states and several foreign countries. Network members are encouraged to forward the electronic notifications we send them to their colleagues to enhance dissemination beyond the existing Network.

The NHLBI HP 2010 Gateway and Health Information Network provide the Institute with a creative approach to engaging Americans in national health objectives; offer a means to disseminate rapidly the latest NHLBI science-based findings and resources for use in clinical and community settings; allow assessment of Government services delivery through customer feedback; and streamline and enable more frequent communication to Network members while significantly reducing significant labor, mailing, and other costs typically associated with traditional methods of communication.

RESEARCH ON LIFESTYLE-RELATED DISEASE FACTORS

Mr. Regula: Some estimate that at least half of all premature deaths are caused by lifestyle related factors such as poor nutrition, unmanaged stress, obesity, sedentary lifestyle and use of tobacco, alcohol and harmful drugs. What portion of NIH-funded research addresses the relation of lifestyle-related factors to disease?

Dr. Kramer: The total NIH FY2001 budget expended on lifestyle related functions to disease was $20.5 billion. The Department of Health and Human Services Report (June 26, 2001) entitled " Behavioral and Social Sciences Research at NIH" estimates that 10% of NIH research funding is currently being used to fund research on lifestyle related factors to dieseases. The report can be downloaded in its entirety at: http://obssr.od.nih.gov/Publications/NIHBSSR2001.pdf.

Specific research specifically on health and behavior or lifestyle-related factors with respect to disease is estimated to be approximately 7% of NIH research funding in FY2001. The estimate includes lifestyle-related factors covering all aspects of a given disease, from prevention through treatment to management of chronic conditions.

ENVIRONMENTAL HAZARDS

Mrs. Northup: Since September 11th, what have we learned about air pollution, asbestos and other environmental hazards? How has that shaped research? How have we disseminated those findings? Are they being coordinated with FEMA?

Dr. Olden: The terrorists' attacks of September 11, 2001 were unprecedented in human history. Although we are all aware of the immediate human toll, the potential exists for long-term health problems for workers who responded to the initial emergency and subsequent cleanup of the site, as well as to the general public. Many of these individuals have been chronically exposed to known toxicants and mixtures of chemical and physical agents of an unknown nature. However, the long-term health effects of inhalation to the combined myriad of pollutants formed by fires, and the collapse of over one million tons of steel, insulation, paper products, office equipment, computers and dust is unknown, as no similar exposure has ever occurred. Toxicological research conducted for the past decades has provided a substantial knowledge base as to the potential health effects from exposure to air pollution, asbestos and other environmental hazards as single chemical entities. As such, acute respiratory effects and more long-term respiratory effects are of great concern. However, the consequences resulting from the combination of exposure and stress associated with the World Trade Center (WTC) attacks on overall physical and psychological health are unknown and require further study.

The NIEHS leadership, staff and grantees determined that there were a number of immediate and long-term needs that would require coordinated planning, execution and analysis to assess the impact on the environment and the health risks to workers and the general population. From our experience, the knowledge base necessary to make informed decisions regarding the health associated with the WTC attacks requires a multidisciplinary, multi-project approach; incorporating exposure assessment with epidemiology studies and mechanisms for public input and communication of information. The research program that NIEHS is supporting, with funds from the 2001 Emergency Supplemental Appropriations Act, is a coordinated multi-project approach. For example, in order to predict, track, and hopefully intervene in some of these problems, collected residues from sites will be analyzed.

NIEHS-supported programs for WTC research, in collaboration with other federal health agencies, will be monitoring area women who were pregnant at the time of the attack. A concern is that the exposures and stress experienced by these women might have an effect on their unborn children. Each child's development will be tracked to determine if any health, learning, or behavioral problems are associated with their exposures while in the womb. Moreover, clinical studies of workers at the WTC will include both clinical and psychological evaluations. It will be important to couple this information with exposure assessment data to more clearly delineate the relationship

between health outcomes and exposure. Respiratory effects in workers and the general public are under study in relation to exposure parameters. The relationship between exposure and symptoms of post-traumatic stress, depression and panic is also being evaluated.

Since September 11, NIEHS-funded research centers have conducted seminars and have developed information packets for the community. For example, researchers have: (1) consulted with the Parents Association of Stuyvesant High School regarding environmental exposures; (2) conducted community forums in different neighborhoods in Manhattan to share information about available resources and services and information about environmental health aspects of the attacks; (3) developed a website with environmental health information for the public; (4) developed a dust reduction brochure for residents; (5) developed fact sheets regarding health concerns for Ground Zero workers, building occupants, and community residents; (6) established an information line to answer questions for workers and the community; and (7) provided consultation to the Port Authority Health and Safety Departments. Additional activities that will be supported include the development of additional educational materials, development of a comprehensive WTC website that addresses WTC environmental health issues, school assistance for emergency response preparedness, risk communication workshops for emergency room personnel and media, and healthcare provider training.

NIEHS has been participating in biweekly conference calls with FEMA on exposure assessment and communication. This has been coordinated via the Health and Human Services (HHS) Office of Emergency Preparedness.

BIOTERRORISM

Mrs. Northup: What is your contribution to the fight against bioterrorism? What have you learned in your years of research that can help us detect and track organisms and the body's response to them?

Dr. Olden: Using 2001 Emergency Supplemental Appropriations Act funds, the NIEHS Worker Education and Training Program (WETP) is developing training modules on various biological and chemical agents. As a first step toward creating a cadre of specialists with expertise in handling Weapons of Mass Destruction, training of remediation workers is a major priority for FY 2003. Based on the work already completed in remediating existing anthrax contaminated buildings, the NIEHS WETP has assisted in the creation of a pool of trained workers with the capability to remediate buildings contaminated with biohazards such as anthrax, smallpox, etc. Also, NIEHS is engaged in rebuilding the hazardous materials and biochemical response capacity of the Fire Department of New York through the immediate implementation of a hazardous materials technician training program in partnership with the International Association of Firefighters, a current NIEHS awardee.

NIEHS has been working with other institutes and agencies to enhance the infrastructure of public health to threats by chemical and biological weapons. NIEHS, whose mission focuses on understanding the burden of human illness and dysfunction from environmental exposures, is planning a program of research related to rapid response to chemical weapon terrorism. The intent of such a program is to support all pertinent areas of investigation that will contribute toward development of specific exposure assessment, therapy, and prevention strategies for diseases/dysfunctions induced by chemical warfare agents. NIEHS proposes a plan that supports both basic and applied research on chemical warfare agents, in which the work would focus on the development of rapid, accurate diagnostics for natural and bioengineered toxicants, effective antioxidant medicines to treat those afflicted, and protective therapeutics for those at risk of exposure.

The NIEHS also funds research in signal transduction and neuroscience that is potentially applicable to the fight against bioterrorism. Another tool is toxicogenomics, a field developed by the NIEHS that combines genomics and toxicology. Once our basic understanding is sufficiently advanced, toxicogenomics technologies can be used in efforts to detect, track and contain chemical poisons or infectious microorganisms. Identification of susceptibility genes and characterization of their function through toxicogenomics can provide importance clues for understanding and ultimately preventing the progression of diseases. The specific pattern of gene response can also provide clues about host defense mechanisms which can also be exploited for prevention.

The remarkable progress that has been achieved through the effort to sequence the human genome and genomes of other organisms has created unprecedented technological opportunities to advance the understanding of the origins of environmentally associated disease, caused by organisms, and toxicity, caused by chemical or physical agents. Primary among these technologies is the capability to utilize gene expression microarrays, and proteomics and metabolomics analyses to characterize the consequences of organism and chemical toxicant insults to humans. It has become possible to establish the signature of altered gene expression from exposure to a single dose of chemicals or to an infectious agent. It is possible, therefore, using these advanced technologies, to develop rapid and early exposure assessments and determine the body's response to these exposures.

SICKLE CELL DISEASE RESEARCH

Mrs. Northup: I am fascinated by your report of using HIV to deliver a therapeutic gene to the bone marrow of mice with sickle cell to cure the disease. What does this tell us about the future of sickle cell disease research?

Dr. Lenfant: Scientists have for the first time corrected sickle cell disease in mice using gene therapy, and this is a very significant research advance. It brings us closer to human gene therapy for what is a very serious genetic blood disorder. Much

more research is needed before the approach can be used in human patients. For example, one important next step is to see how effective this vector is in larger animals that are more similar to humans. Second, it will be important to assess the safety of the HIV-based gene transfer vector when it is produced in large quantities - in particular with respect to its ability to replicate. Third, the toxicity of the regimen used to partially destroy the bone marrow of the transplant recipients before they receive genetically corrected bone marrow must be addressed. The first human application of gene therapy for sickle cell disease would be done with autologous transplantation. In this procedure, some of a patient's own bone marrow cells would be removed and genetically corrected. The remaining original marrow would then be partially destroyed to "make room" for the genetically altered cells, which would be returned to the patient. Currently, the drug and/or radiation treatments used to partially destroy a patient's marrow have an associated risk of toxic side effects that is unacceptably high. A number of research studies are under way to develop less toxic regimens that would still allow the new bone marrow to produce normal red blood cells for the long term. So, in summary, human application of gene therapy to cure sickle cell disease may still be several years away.

In the meantime, research will continue on other types of therapy that either cure or reduce the severity of sickle cell disease. Currently, the only available cure is bone marrow transplantation. In this procedure, a patient receives a transplant of bone marrow from a healthy, genetically compatible ("matched") sibling donor. However, only about 18 percent of children with sickle cell disease have such a donor available. For other children and adults with the disease, treatment includes transfusions, which correct anemia and prevent strokes, and pain-killing drugs. In addition, a drug called hydroxyurea is used in adults to reduce the frequency of painful crises and acute chest syndrome. The drug's use in children is still being studied.

CORD BLOOD

Mrs. Northup: What can you tell me about research regarding the use of cord blood in stem cell research? What is the prevalence of cord blood use?

Dr. Lenfant: In 1992, the NHLBI awarded a grant to the New York Blood Center to develop a bank of placental/umbilical cord blood units for transplantation to unrelated humans. In the ensuing 10 years, cord blood banks around the world have amassed more than 40,000 cord blood units and facilitated more than 2000 transplants for patients with 60 different diseases. In 1996, NHLBI began a national multicenter study of cord blood banking and transplantation to examine the effect of cell dose and degree of human leukocyte antigen (HLA) mismatch on patient outcome.

Most cord blood transplants have been performed in children because they can get by with the relatively small cell dose in a cord blood unit. Research is under way to determine whether increasing the number of cord blood cells by growing the cells in culture will improve transplant outcome for children and increase the feasibility of cord blood transplants for adults.

The ability of cord blood stem cells to contribute to the development of other tissues is an exciting new field with potential for clinical applications for a wide variety of diseases including heart disease, diabetes, and diseases of muscles and the central nervous system. Expanding research in basic stem cell biology will hasten our understanding of the potential of these cells to lead to new treatments for patients.

More than 2000 unrelated-donor cord blood transplants have been performed worldwide since 1992. The majority of these have occurred in children with hematologic malignancies, but some have also been performed in patients with inherited hematologic disorders (e.g., Fanconi anemia, sickle cell disease) and inborn errors of metabolism. Because it is possible to perform transplants using cord blood units matched at only 4 of 6 possible HLAs, the probability of finding an acceptable donor unit is more than 90 percent.

Most cord blood transplants use volunteer unrelated-donor units stored in public banks. However, because patients with sickle cell disease and thalassemia have a special need for matched donors, NHLBI supports a program that banks cord blood from healthy, HLA-matched siblings of these patients. Six such patients have received transplants with units from this bank.

For pediatric patients, use of cord blood as a source of donor cells has increased dramatically. In some pediatric transplant programs, the number of cord blood transplants equals or exceeds the number of unrelated-donor marrow transplants. However, other pediatric transplant programs still predominantly use marrow. We estimate that approximately 20 unrelated cord blood transplants are performed per month for pediatric patients in the United States.

Cord blood is viewed as a last resort for adult patients who need a transplant but do not have another donor. This is because of the small cell dose and associated delay in neutrophil and platelet engraftment for cord blood transplants compared with marrow or peripheral blood stem and progenitor cell transplants. Options under investigation to improve the outcome of cord blood transplants in adults include using more than one unit for transplantation and culturing the cord blood to increase the number of available cells.

RESEARCH ON COLLEGE DRINKING

Mrs. Northup: The Washington Post reported this morning on the problem of underage and binge drinking on college campuses. The article mentioned that few campus programs aimed at reducing drinking have been tested scientifically to determine whether they work. What are you doing to correct this gap in research, and, specifically, are there plans for research in college communities?

Dr. Kington: In 1998, recognizing that few attempts by colleges to reduce the consequences of drinking on their campuses had been successful, NIAAA brought together 11 college presidents and 12 alcohol researchers to form the Task Force on College Drinking. NIAAA's reasons for forming the Task Force were threefold: (1) to provide high-school and college administrators, students, parents, community leaders, policymakers, scientists, and the beverage industry with research-based information about the nature and extent of dangerous drinking; (2) to offer college and university presidents recommendations on the potential of current strategies to reverse the culture of drinking on campus, and (3) to offer the research community, including NIAAA, recommendations for future investigations on prevention of hazardous drinking by college students. The Task Force commissioned 24 scientific papers to begin to fill the gaps in the research base, identified research needs, issued recommendations for both colleges and researchers, and distributed outreach material.

While the Task Force was preparing its report, NIAAA continued to fund prevention and intervention studies. A Multi-Campus Comprehensive Prevention Study, currently underway at 16 campuses of the two California university systems, is an example of the kind of college-community studies recommended by the Task Force.

DENTAL AMALGAM

Mrs. Northup: Can you give us the results of the most recent research on dental amalgam? Are we taking unnecessary risks by using mercury in dental fillings? Are there alternative dental compounds and what are the risks or costs associated with their use?

Dr. Tabak: There have been no major recent findings on the health effects of dental amalgam. However, NIDCR continues to support two large studies in the Northeastern United States and Lisbon, Portugal, collectively termed the Children's Amalgam Trial. Each involves approximately 500 children, and they are in their second and third year of followup, respectively. Results from these studies, which are monitored annually by an independent Data and Safety Monitoring Board, have yet to show any adverse effects of dental amalgam as compared to a composite restorative material using a broad array of outcome measures, including those in the physiological, neurological, cognitive, and behavioral domains. Even the increase in levels of urinary mercury in the groups receiving amalgam restorations appear to remain in what has been viewed as a normal range.

A third trial, funded independently of the Children's Amalgam Trial by the NIDCR, is examining potential neurological and neuropsychological deficits using a cross-sectional approach with adults as participants. The investigators in this study are examining neurological function, visual/spatial ability, self-reported mood, along with functions related to memory and attention in approximately 550 adults, aged 30-49 years. While the study has recently been completed, results have not yet been published. Nevertheless, it is our understanding that there were no deleterious health effects attributable to dental amalgam in this group of adults.

Based on the clinical trials cited above as well as on several epidemiological studies, we believe that other than the rare case of a mild allergic response resulting from contact with the material, there are no deleterious health effects attributable to dental amalgam in humans.

We are not taking unnecessary risks by using mercury in dental fillings. Dental amalgam has been used for more than 150 years. Indeed, for many years, it was the only restorative material available. Amalgam's popularity among oral health professionals stems from its easy and efficient applications (i.e., it is malleable at room temperature), its ease of storage (i.e., it does not require special environmental controls for its safe storage), its longevity *in situ*, its ability to maintain normal function of filled teeth, and its low cost. However, over the years, additional materials have been developed for use as dental restoratives including dental alloys (including noble alloys that are gold- and palladium-based and base metal alloys that are nickel- and cobalt-based), resin composites (consisting of dimethacrylate and silica - containing reinforcing materials) and porcelain ceramics.

After decades of research, the scientific evidence strongly indicates that amalgam is a safe dental restorative. Nevertheless, the NIDCR has supported studies on the development and testing of alternative restorative materials. One NIDCR-supported research team has been developing a non-mercury direct metallic filling material. However, successful use of the material requires the use of special techniques and thus it is likely to be relatively expensive and unlikely to be adopted by dentists for widespread use.

In determining whether Americans are taking unnecessary risks by using non-biologic material, including amalgam, it is important to note that, for many individuals, amalgam might be the only viable option because of cost or other factors affecting availability. At this point, particularly for low income Americans who might need restoratives the most, it appears that there are significant limitations in the use of an alternate material due to the direct costs of the restoration, the longevity of the material *in situ*, and the ability to store and use the material in remote sites that are often limited in terms of staffing and facilities.

There are other alternative dental restoratives, each of which has been developed to address a specific clinical issue (e.g., aesthetics, wear characteristics, ease of use, extent of use). These include dental alloys such as noble alloys that are gold- and palladium-based as well as base metal alloys that are nickel- and cobalt-based, resin composites consisting of dimethacrylate and silica containing reinforcing materials, and porcelain ceramics typically used in crowns. Part of the 1993 report, "Dental Amalgam: A Scientific Review and Recommended United States Public Health Service (USPHS) Strategy for Research, Education and Regulation," of the Public Health Service Subcommittee on Risk Management of the Committee to Coordinate Environmental Health and Related Programs dealt with a comparison among three of the leading restorative materials.

The report indicated that there are alternative materials that can replace dental amalgam in many traditional clinical situations, particularly in low stress-bearing areas of the tooth. However, on a one-time use basis, none of the materials is less costly than dental amalgam. A model predicting cumulative costs of a restoration of a posterior tooth over the past 60 years was developed for the USPHS report. When indicators such as the cost of the initial placement and clinical life expectancy of the restoration were assessed, all alternatives were found to be more expensive than amalgam. For example, composite and glass ionomer restoratives were estimated to be approximately 1.5 times the cost of amalgam, gold foil 4 times the cost, cast gold alloy 8 times, and metallic-ceramic crowns 8 times more expensive.

It is important to note that there is no single restorative material available that could reasonably substitute for dental amalgam in all situations. While amalgam may be esthetically less acceptable than other materials, it is useful and clinically appropriate in a wide variety of situations. Because of its relative low cost, its ease of storage and preparation, its relative durability, versatility, and ease of use by dental professionals, and importantly its safety track record of safe, amalgam is likely to remain as the material most in demand for use as a dental restorative.

PERIODONTAL DISEASE AND PRE-TERM, LOW-BIRTH WEIGHT BABIES

Mrs. Northup: I am interested in the relationship between periodontal disease and a host of other diseases. Specifically, what can you tell me about research on the relationship between: Periodontal disease and pre-term, low-birth weight babies?

Dr. Tabak: Pre-term birth and low-birth weight are considered the leading perinatal problems in the United States. NIDCR-supported investigators have been at the forefront in demonstrating potential associations between periodontal disease and these perinatal problems. Recent studies indicate that a woman may be 3 to 8-fold more likely to deliver a pre-term low-birth weight baby if she has moderate to severe periodontal disease. In one NIDCR-funded study, investigators have found that pregnant women who fail to mount a strong antibody response against the microorganisms that are implicated in periodontal disease are at a significantly higher risk for premature delivery. This is consistent with the concept that maternal antibody has a protective effect and favors full-term delivery. In another NIDCR-funded study, a clinical trial is being conducted to determine if treating periodontal disease will lower the risk of delivering pre-term low-birth weight babies. The results of this trial demonstrate that treatment by simply cleaning the teeth significantly reduces the incidence of pre-term births. Of major interest, however, is the finding that somewhat more extensive treatment, scaling and root planing, dramatically reduces pre-term births. If this proves true to the general population, a simple intervention of scaling and root planing teeth may be used to reduce the number of premature babies born in this country.

PERIODONTAL DISEASE AND TOBACCO USE RELATIONSHIP

Mrs. Northup: I am interested in the relationship between periodontal disease and a host of other diseases. Specifically, what can you tell me about research on the relationship between: Periodontal disease and use of tobacco?

Dr. Tabak: A number of studies have implicated smoking in the development of periodontal disease. NIDCR-supported research has shown that the severity of the disease correlates with the self reported level of smoking. In exploring this issue in more detail, NIDCR-funded investigators have demonstrated that the level of serum cotinine, which serves as a reliable biomarker for smoking status, parallels the magnitude of periodontal disease. Furthermore, this same team of investigators has shown that significantly greater numbers of known periodontal pathogenic bacteria are harbored in the mouths of smokers than found in non-smokers. This finding may, at least in part, explain the increased risk for periodontitis observed in smokers. In addition, smoking decreases the activity of neutrophils, cells that play a major role in defending the body, including the oral cavity, against pathogenic bacteria. The levels of antibodies that protect against pathogenic bacteria are also lower in smokers than in non-smokers.

The use of smokeless tobacco also has deleterious effects on oral tissues. Unlike cigarette smokers, who experience widespread periodontal damage, the oral effects of smokeless tobacco are localized to the site of placement. The periodontal alterations in smokeless tobacco users are recession of the gums and loss of tooth attachment at the relevant sites.

PERIODONTAL AND HEART DISEASE RELATIONSHIP

Mrs. Northup: I am interested in the relationship between periodontal disease and a host of other diseases. Specifically, what can you tell me about research on the relationship between: Periodontal disease and heart disease?

Dr. Tabak: The extensive blood and lymph circulation of the orofacial complex provides a critical link between the mouth and the rest of the body. Thus, the health status of the mouth may well affect the health status of other sites in the body. Periodontal disease is one of the most common chronic infections in man and results in increased prevalence and severity of bacteremia. The bacteria that have gained entrance from the oral cavity and mediators released by their interactions with cells and tissues may well be implicated in a number of systemic diseases including those affecting the cardiovascular system. NIDCR is supporting studies to explore a potential relationship between periodontal and cardiovascular diseases. In this endeavor, the NIDCR is working closely with other NIH Institutes and Centers.

CARE FOR CANCER PATIENTS

Mrs. Northup: Have you conducted any research on the relationship between nursing and caring for cancer patients? What has that research shown about emerging strategies for caring for cancer patients?

Dr. Grady: Yes, nursing research on chronic conditions such as cancer focuses on promoting screening for the disease, management of disease and treatment symptoms, improving quality of life for the patient and the family caregiver, and palliative care up to the end of life. Let me give you some examples:

To understand more about motivations that lead to genetic screening for breast cancer, investigators developed a study that offered education, counseling and family-based BRCA 1 and 2 screening tests to women at increased risk of breast cancer. The study assessed reasons why women participate in the intervention. Eighty percent said they attended to learn about the test, 43% to have the test, and 38% to help research. After the intervention, 83% intended to ask their affected relatives to be tested, but only half of the relatives came for pretest counseling. Following up on this study, the investigators determined that only about 18% of women with a genetic predisposition to breast or ovarian cancer were willing to participate in randomized studies of risk factor reduction. However, most were willing to participate in nonrandom studies, indicating that the latter studies may be more feasible for women at risk.

Ongoing research relating to functioning and quality of life includes a focus on breast cancer survivors. Studies are being done in postmenopausal survivors to determine the effects of exercise and/or raloxifene on such factors as bone density, muscle strength, fatigue, and quality of life. The results of these studies have the potential to reduce morbidity and healthcare costs that confront these survivors. Other research studies compare two exercise interventions -- aerobic and resistance -- to reduce cancer-related fatigue in patients receiving chemotherapy. The goal is to reduce treatment side effects, particularly fatigue, physical decline, and debilitation. Additional research combines exercise and psychosocial support and the effects on the immune system.

Strategies for caring for cancer patients include not only symptom management, but also management of treatment side effects. Additional research involves how cancer treatment affects physical functioning, symptoms, caregiver assistance, and utilization of healthcare services. Emphasis is given to understanding patient problems and how to design interventions that would effectively involve family caregivers. Regarding our end of life research, studies are under way to address appropriate interventions for patients and families. One example is that of a telephone or computer support intervention for older caregivers of dying cancer patients.

ENVIRONMENTAL TRIGGERS

Mr. Obey: Recent studies have shown that the environment accounts for a substantial portion of the risk for several chronic diseases, such as Parkinson's, autoimmune diseases, asthma, Alzheimer's, and cancer. What new initiatives does NIEHS have underway to find the environmental triggers associated with these diseases?

Dr. Olden: The NIEHS has advanced a new initiative on Parkinson's Disease (PD) in FY 2002 with a consortium of collaborating research centers for PD which looks closely at the environmental triggers associated with the expression and progression of PD. The NIEHS developed a unique initiative on the fetal basis of adult disease that focuses research on the environmental triggers that may be operating in the intrauterine environment. This program is looking closely at susceptibility to neurodegenerative/neurodevelopmental-based diseases such as Alzheimer's Disease and autism; pulmonocardivascular disease; which includes asthma; and functional and structural birth defects, including those with enhanced susceptibility to cancer. A specific initiative has also been launched on environmentally-induced cardiac malformations. The NIEHS neurotoxicology program is also a participant in the FY 2002 trans-NIH initiative for Autism Research Centers of Excellence (STAART Program). NIEHS has also continued its participation in the trans-NIH initiative on Biological Mechanisms of Age-Related Prostate Growth which seeks to understand the role that environmental exposures may play in prostate disease and cancer. NIEHS is developing a new initiative on the role of environmental exposures in the onset and progression of breast cancer. This newly awarded Toxicogenomics Research Consortium currently supports experiments that will provide an understanding of the expression profiles of DNA repair and other genes that are involved in mammary carcinogensis.

The NIEHS is interested in the interactions between innate susceptibility and environmental influences in the causation of disease and is involved in several ongoing efforts in the specific area of autoimmune disease:

- gene-environment interactions in the pathogenesis of systemic lupus erythematosus, particularly in relation to occupational exposure and hormonal influences.

- effects of indoor allergens, derived, for example, from dust mites and cockroaches, on the pathogenesis and course of pediatric asthma.

- efforts within the Office of Clinical Research, the Environmental Autoimmunity Group, are underway to research a broad program of clinical and basic investigations in the area of adult and pediatric autoimmune disease. The current focus is on the myositis syndromes, a heterogeneous group of disorders defined

by chronic muscle inflammation, as prototypic autoimmune diseases. These studies include epidemiologic surveys, molecular genetic studies and clinical investigations in disease pathogenesis, as well as the development of clinical tools for assessment of innovative therapies.

In addition, the continuing trans-NIH autoimmune disease research initiative, in which the NIEHS is a key player, will convene in early 2003 to document progress and to determine new research initiative directions.

CHILDREN'S ENVIRONMENTAL HEALTH

Mr. Obey: It is my understanding that NIEHS, in cooperation with EPA, has been co-funding several Centers of Excellence for Children's Environmental Health. What have we learned from these Centers and what are your plans regarding the future of these Centers since a number of them are in the fifth and final year?

Dr. Olden: NIEHS, in collaboration with EPA, has funded eight Centers for Children's Environmental Health and Disease Prevention since 1989 and added four new Centers to the network during September 2001. This highly successful multidisciplinary program brings together biologists, toxicologists, geneticists, epidemiologists, environmental health scientists, behavioral scientists, and community partners to explore the role of environmental exposures, such as indoor and outdoor air pollutants, pesticides, metals, and other prevalent neurotoxicants, on the growth and development of young children, and their risks of asthma and other respiratory diseases and developmental disabilities such as autism, learning disabilities and hearing loss. Intervention/prevention research within a community-based participatory research framework is the cornerstone for translating scientific findings to communities at risk in these research Centers.

In less than five years, these centers have made significant contributions to the knowledge of the molecular basis of action for environmental triggers of asthma, the sensitivity to organophosphate pesticides in young children, and the neuroendocrine effects of PCBs and chlorpyrofos. Research teams are contributing important information on useful intervention strategies that can reduce the "take-home pathway" in agricultural workers so that children of workers will not be exposed to high levels of organophosphate pesticides when they are the most susceptible. Intervention studies, which employ trained community workers, have been successful in educating residents about cleanup protocols for reducing home allergens from dust mites and cockroaches and using less pesticides in their homes to effectively rid them of environmental triggers. Research teams that include community members are being very successful in leveraging support for this work from community sources and are providing sustainable models for future environmental health education and advocacy.

NIEHS plans to continue this highly successful program by announcing a competition for new applications in the fall of 2002. Additional research on all of the topic areas would increase our knowledge base on the health effects in children due to early life exposures to environmental chemicals and other agents. A sustained research effort is needed to understand the environmental triggers that cause autism, learning disabilities, asthma and other conditions that affect children. NIEHS would like to extend the research started in the Children's Centers Program by providing future opportunities for translation of these important research findings to affected communities, health care practitioners, and policymakers.

TOXIC CHEMICALS, THE ENVIRONMENT AND BREAST CANCER

Ms. Pelosi: Between 1991 and 1999 we have seen an alarming increase in breast cancer rates in Marin County. It is my understanding that there are some known risk factors that contribute to higher risk of breast cancer, including alcohol consumption, early puberty, age at first pregnancy, and late menopause. However, even when these known risk factors are taken into account, over half of all breast cancer cases remain unexplained. Last month, I introduced a bill to create a nationwide health tracking network that will identify the links between chronic disease and exposure to environmental pollutants. The information that is eventually collected from this network will provide critical information on exposures and related health outcomes. What research is NIEHS currently doing to understand the link between exposure to toxic chemicals and the environment? Is any of this research specifically focused on breast cancer?

Dr. Olden: NIEHS has taken an active role in supporting research that develops new methods to measure chemicals in the environment and study the link between environmental exposures and human body burden. The field of exposure assessment is getting more attention as we realize that new technologies becoming available rapidly, provide a unique opportunity to gather data on the low levels of chemicals to which populations are exposed and to look at the effects of these chemicals on cellular and molecular processes that relate to human disease. Technologies such as geographic information systems offer new tools to track environmental pollutants at the community level, providing an ecologic exploration of trends and associations. At the other end of the research spectrum, toxicogenomics offers the possibility to explore the human genome looking for unique patterns of genetic response to specific chemical exposures. NIEHS currently supports research across this entire continuum. For example, over past decades NIEHS-supported research has significantly contributed to our understanding of the health effects of chemicals such as arsenic, lead, endocrine disruptors such as pesticides and phthalates, and complex mixtures such as air pollution by supporting the methods and technology development to assess such exposures in ecosystems and in human biospecimens. We have supported the development of exposure biomarkers that have been validated in exposed populations and are currently being employed in many epidemiologic studies of human populations at risk of environmentally-related diseases.

Measurement error due to inaccurate exposure assessment is the weakest link in epidemiologic studies of human populations at risk for complex diseases, including breast cancer. Improvements in measurement techniques so as to more accurately quantify a woman's exposure to chemicals and other exposures over her lifespan is critical to understanding how these chemicals impact the developing mammary gland, the hormonal environment, and a women's future breast cancer risk. NIEHS has supported state-of-the-art epidemiologic studies of environmental chemicals and breast cancer risk, and is currently supporting several grantees working directly to improve exposure assessment techniques. Studies during pregnancy are ongoing and will soon provide new information on exposures to pesticides, phthalates, and polyaromatic

hydrocarbons in pregnant women and their offspring. Future follow-up of these infant daughters through puberty will be essential in identifying girls at future risk of breast cancer. Follow-up of the mothers, on whom excellent exposure data will be available, will help define breast cancer risk in relation to exposures during critical windows of susceptibility. In addition, research in Michigan girls who were exposed to polybrominated biphenyls (PBBs) in utero has demonstrated an association with early onset of menarche, which is a risk factor for future breast cancer.

NIEHS also has supported a number of mechanistic laboratory-based research studies of the effects of these key exposures in mammary gland carcinogenesis. This work seeks to understand the cellular and molecular effects on signaling and other pathways, enzyme function and gene expression and function at cell cycle control, points critical to breast carcinogenesis.

GENES AND THE ENVIRONMENT

Ms. Pelosi: Dr. Collins, one of these benefits of our new understanding of the human genome is a better sense of the interaction between genes and the environment, and how that interaction can lead to disease. What do we know so far about those interactions and their relationship to adverse health outcomes? Is your Institute working with NIEHS in this area?

Dr. Collins: It is known that both genetic and environmental factors contribute to the development of nearly all human diseases. The degree of contribution of one type of factor compared to the other varies widely among different diseases. With our increasing knowledge of human genetics, as a result of the availability of the human genome sequence, several clear examples of the interplay of genetics and environment have emerged. It has been known for some time that a low folic acid diet during pregnancy is associated with a higher risk of neural tube defects and spina bifida in the infant. It has now been shown that there are genetic variations in the genes that encode the enzymes involved in folic acid metabolism, and the risk of spina bifida appears to be highest in infants born to mothers with a particular variant. This knowledge may ultimately allow physicians to screen women for the presence of the particular variation; those found to carry the susceptibility variant can then be advised to maintain a diet high in folic acid during pregnancy.

A second example concerns variants in the gene for a clotting factor called Factor V. Women with a common variation called Factor V Leiden have an increased risk for potentially fatal cerebral vein thrombosis if they are taking birth control pills. Again, this knowledge may ultimately allow physicians to screen women who would like to use the birth control pill to determine who among them would be at risk for severe side effects.

NHGRI and NIEHS have collaborated on several projects--for example: the newly designed haplotype map of the human genome, the full length cDNA project (called MGC or the Mammalian Gene Collection), and the mouse genome sequencing consortium. NHGRI and NIEHS staff have also had many discussions about the Environmental Genome Project and share relevant information with each other regularly. We also share common interests in many of the ethical, legal and social issues surrounding genetic research and there has been frequent interaction between staff of the two institutes on these topics.

THE NURSING SHORTAGE

Ms. Pelosi: We keep hearing about the nursing shortage in our country. What are some of the effects on patients? What is the effect on nursing research? Is NINR conducting research that could help ease the shortage?

Dr. Grady: NINR is working to address the issues related to the nursing shortage, particularly in the nation's hospitals. NINR-funded research has found strong, consistent relationships between nurse staffing and patient outcomes for both medical and surgical patients. Outcomes influenced include pneumonia, upper gastrointestinal bleeding, shock, urinary tract infections, and length of stay. The study, called Nurse Staffing and Patient Outcomes in Hospitals, is based on 1997 data from more than 5 million patients from 799 hospitals in 11 states. NINR, the Agency for Healthcare Research and Quality, the Centers for Medicare and Medicaid Services and the Health Resources and Services Administration were all involved in this study, which was conducted by the Harvard University School of Public Health. Findings indicate that higher RN staffing was associated with a 3 to 12% reduction in certain adverse outcomes.

A nursing shortage could negatively impact on the number of future nurse researchers available to conduct studies that add to the scientific base for nursing practice. The main cause is fewer enrollments in nursing education programs. In 2001, enrollment in nursing entry-level baccalaureate programs increased slightly by 3.7% over 2000 -- ending a six-year period of decline, but still 17 percent below the 1995 enrollment by over 21,000 students. Another reality is a shortage of nursing school faculty. According to a recent survey of the American Association of Colleges of Nursing (AACN), 39 % of schools indicated faculty shortages as a reason for not accepting all qualified, entry-level applicants. They further cite the average age of doctorally-prepared nurse faculty as 54 years. Significant faculty retirements are expected within the next 7 to 10 years.

NINR is conducting research that could help ease the shortage, particularly in hospitals, to identify problems and devise solutions. Recently, a large research project studying hospitals in five countries, including the U.S., identified low morale among these nurses, including job dissatisfaction, burnout and intentions to leave the profession. In the U.S., nurses appear to be more dissatisfied with working conditions

than with wages. They cite increased patient loads and inappropriate tasks, such as cleaning rooms -- with insufficient time left for patient education, as among the key issues needing resolution. They indicate that hospitals are not organized properly, and more research is needed to measure the effects of hospital organization and nurse staffing levels and mix on patient outcomes.

NINR is also supporting initiatives to help ensure a stable scientific workforce for the future through several training opportunities. Programs are being expanded to attract young students to research careers, including placing them in ongoing research projects; promote faculty and research-intensive environments through centers programs; and target schools with developing research programs that have not had major NIH support. Since minorities only represent 12.3% of the RN workforce, NINR is emphasizing research career development of minority nurses both to enrich workforce expertise and to conduct research on reducing health disparities. In particular, we support programs that encourage research depth to address key national health issues related to chronic illness, genetics, health disparities, end-of-life/palliative care, and health promotion/disease prevention.

HIV/AIDS-TB COINFECTION

Ms. Pelosi: Dr. Lenfant, HIV/AIDS-TB coinfection is a significant health concern in my district and around the world, especially in developing countries. I understand the NHLBI sponsors research on the interaction of AIDS and TB. Can you please update me on the HIV/AIDS-TB research your Institute is supporting?

Dr. Lenfant: The NHLBI supports a broad spectrum of research on HIV/AIDS-TB, including educational and behavioral research, studies of interactions of TB and HIV in isolated preparations of human cells, and development of theoretical and animal models to examine the complex synergy between these two diseases.

The TB Academic Award program provided funds to 29 medical schools throughout the country for TB curriculum development. Each of these programs stressed the recognition of dual HIV-TB infection, the increased risks associated with it, and the importance of completing prophylactic treatment to prevent active TB, especially in HIV-infected patients. A randomized, controlled study in a homeless population in San Francisco with a high rate of HIV infection found that a $5 bi-weekly incentive improved adherence to treatment and that residence in a hotel or apartment was also associated with completion of therapy. Other behavioral studies are focusing on inner-city populations with high rates of TB-HIV infection and on immigrants from regions of the world with a high prevalence of TB. Educational studies are seeking to improve communication between health providers and TB patients and to improve patient adherence to treatment. For example, the NHLBI supports a clinical trial in Harlem, a community with high rates of TB-HIV dual infection, to compare the efficacy and cost-effectiveness of an experimental intervention to improve current clinical practice for treatment of latent TB. The experimental intervention focuses on the patient's perception of susceptibility,

severity, benefits, preservation of health, barriers, and self-efficacy; it uses peers, who themselves have been treated for latent TB, to assist the patients and provide them with much-needed role models.

NHLBI-supported scientists are determining the effects on the host lung defenses of dual HIV-TB infection. HIV and TB both infect lung macrophages, the cells that serve as the first line of defense to protect the lung from infections. Successful protection against TB infection in the lung requires participation of both lung macrophages and lymphocytes.

NHLBI-supported research on dual TB-HIV infection has now been expanded to non-human primate models making it possible to explore, in depth, the molecular interactions between the two infectious agents, something that cannot be accomplished from clinical observations or studies in mice. Mathematical techniques are being developed and employed to understand the multiple factors that control, activate or facilitate the immune response to the two infections. The Institute also continues to fund studies aimed at determining the nature of the immune responses in the lung to TB and to HIV individually, neither of which is fully understood.

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

Ms. Pelosi: As you know, Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death in the United States, behind heart disease, cancer and stroke. In spite of this, many Americans do not know exactly what COPD is or how to prevent it. I understand that your Institute is involved in Global Initiative for Chronic Obstructive Lung Disease or GOLD. Can you please tell me what GOLD is and how it hopes to change perceptions of Chronic Obstructive Pulmonary Disease (COPD)?

Dr. Lenfant: COPD is a major public health problem not only in the United States but worldwide. To focus attention on it, the NHLBI, in conjunction with the World Health Organization and a number of experts drawn from the United States and abroad, began the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 1997. Its objectives are to increase awareness among the medical community, public health officials, and the general public that COPD is a public health problem; to promote study of the reasons for the increasing prevalence of COPD, including the role of environmental exposures; and to recommend and implement effective prevention, diagnosis, and management strategies for use in all countries in order to decrease morbidity and mortality from COPD. Although today the World Health Organization is no longer actively with the program, the GOLD has accomplished much to date, including making available to the public and the medical community the document "Global Strategy for the Diagnosis, Management, and Prevention of COPD" and a compact pocket guide for ready reference on COPD management for practicing physicians. In addition, a Web site for GOLD has been set up to facilitate communication internationally and to provide computer access to both the

evidence-based management guidelines and the supporting evidence. Approximately 70 countries are active participants in, and users of, the GOLD program. In the United States, GOLD has implemented a coalition of professional and voluntary organizations committed to the control of COPD and to the support of patients with that disease.

Updating the GOLD guidelines and developing further educational materials are among the major activities planned for the next phase of GOLD. The NHLBI has placed the GOLD guidelines report on its Web site, along with a "palm pilot" program to facilitate widespread use of the guidelines. Through GOLD and other activities, the NHLBI hopes to help the millions of people who suffer from COPD and its complications.

DISEASE PREVENTION AND PUBLIC EDUCATION

Mrs. Lowey: Recently, Secretary Thompson announced research showing that walking 30 minutes a day, five days per week can significantly reduce the rate of type 2 diabetes. This kind of information is so vital - the public needs to be aware of steps they can take to reduce the incidence of chronic disease. Unfortunately, so much of the research NIH does is not effectively transmitted to the public. What can we do to better inform the public about the great research you do, particularly in the area of prevention?

Dr. Kirschstein: The NIH strives to make the public aware of effective strategies to prevent disease and is continually developing programs to reach the public about new and important research findings. NIH currently has a number of public health education and outreach programs to inform the public about effective interventions to prevent and control chronic diseases. In addition, Secretary Thompson's "One Department" initiative to consolidate HHS' Public Affairs Offices will greatly assist in ensuring that the public receives a strong, clear, cohesive message on key health issues.

Informational material on effective health interventions is posted at Institutes' websites and distributed in pamphlet form. Specific examples include:

- National Diabetes Education Program (NDEP): The NDEP is a partnership between the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the Centers for Disease Control and Prevention, and more than 200 public and private organizations. A major goal of NDEP is to increase public awareness of the seriousness of diabetes, its risk factors, and strategies for preventing diabetes and its complications. Based on the positive results of the Diabetes Prevention Program (DPP) study that you mentioned, the NDEP is focusing its efforts on the message that it is possible to prevent or delay type 2 diabetes with moderate exercise and changes in diet. Secretary Thompson is working to promote prevention of all chronic diseases and has held two press conferences focused on the results of the DPP, in August of 2001 and in March of 2002. Each press conference garnered a great deal of press coverage and helped to publicize the findings of the DPP.

- 5-A-Day For Better Health Program: A national program to increase Americans' consumption of fruits and vegetables to 5 to 9 servings a day to promote good health and reduce the risk of cancer, heart disease, hypertension, diabetes, obesity and many other diseases. As the largest public/private partnership for nutrition in the country, the Program's strength comes from the combined efforts and resources of the National Cancer Institute, Produce For Better Health Foundation, Centers for Disease Control and Prevention, United States Department of
  Agriculture, American Cancer Society, Produce Marketing Association, United Fresh Fruit and Vegetable Association, National Alliance for Nutrition and Activity.

- Cancer Information Service "hotline" (1-800-4-CANCER): The NCI has developed and maintains the Cancer Information Service "hotline" for questions from the public regarding preventing, screening for, treating, and surviving cancer.

- NCI Physicians Data Query (PDQ): The PDQ is a web-based knowledge center with state of the art information on prevention, screening, and treatment of a broad range of cancers. It is updated monthly and carries both health professional and lay person versions.

- Milk Matters Calcium Education Campaign: The National Institute of Child Health and Human Development (NICHD) "Milk Matters Calcium Education Campaign" works to educate kids, parents, and health professionals about the importance of getting enough calcium during the childhood and teen years.

- "Back to Sleep": A NICHD campaign that educates about the importance of putting babies on their backs to sleep to help reduce the risk of Sudden Infant Death Syndrome (SIDS).

- WISE EARS!: The National Institute on Deafness and Other Communication Disorders (NIDCD) sponsors an initiative for the prevention of noise-induced hearing loss.

- Weight Control Information Network (WIN): WIN, a health information program of the NIDDK, is developing science-based information about the overall health benefits of regular exercise and healthy eating for health care providers and the public, including parents with children who are overweight and at risk for developing type 2 diabetes.

- Hearts N' Parks: A national, community-based program supported by the National Heart, Lung, and Blood Institute (NHLBI) and the National Recreation and Park Association (NRPA). This innovative program aims to reduce the growing trend of obesity and the risk of coronary heart disease in the U.S. by encouraging Americans of all ages to aim for a healthy weight, follow a heart-healthy eating plan, and engage in regular physical activity. It is one component of the NHLBI Obesity Education Initiative.

- National Eye Health Education Program (NEHEP): The National Eye Institute in partnership with more than 65 national organizations. The goals of the NEHEP are to 1) prevent vision loss through early detection among high risk audiences including older adults, Hispanics, African Americans, and American Indians/Alaskan Natives and 2) promote the role and value of vision rehabilitation in maintaining independence and quality of life for those who have lost vision due to eye disease.

- Translational Research for the Prevention and Control of Diabetes: The NIDDK, the NEI, the National Institute of Nursing Research, and the American Diabetes Association are sponsoring a Program Announcement to encourage research in translation of recent scientific advances into prevention and treatment for type 1 and type 2 diabetes. This mechanism particularly encourages interventions that focus on translating new advances into practice in underserved and minority populations.

The NIH serves as a resource agency along with other agencies charged with translation of effective medical and public health science into practice. For example, the NIH is one of the lead agencies in the development of the Healthy People 2010 report to the Nation. This document, produced by the Department of Health and Human Services, describes systematic approaches to health improvement and lists leading health indicators, achievable objectives, and outcome measures. It is widely used by state health departments in development of health programs.

The NIH also serves as a resource agency for the Guide to Clinical Preventive Services (issued by the Agency for Healthcare Research and Quality) and the Guide to Community Preventive Services (issued by the Centers for Disease Control and Prevention).

The NIH continues to develop new and appropriate health promotion programs to increase public awareness of effective disease prevention. In addition, the complementary activities of the CDC serve the public health promotion need. The CDC is another principal federal agency for providing information to enhance health decisions, and for promoting health. CDC serves as a national focus for developing and applying disease prevention and control, environmental health, and health promotion and education activities designed to improve the health of the people of the United States.

BREAST CANCER AND THE ENVIRONMENT

Mrs. Lowey: Dr. Olden, as you know, I am very interested in the link between breast cancer and the environment. I have again introduced legislation to provide $30 million per year over five years for NIEHS to study this link. The committee also included language in last year's bill calling for NIEHS to increase this research. You and I have met on this issue, and I want to be sure to mention that you have been very helpful and supportive. We are exposed to thousands of chemicals, compounds and toxins every day which may cause different diseases. We also do not fully understand how environmental exposures act as the trigger for genetic predispositions to many diseases, including breast cancer. What is currently underway at NIEHS to study this link between breast cancer and the environment? How can we work together to further this important research?

Dr. Olden: NIEHS has actively supported research on the effects of environmental chemicals and other exposures on breast cancer risk for the past eight years. Our research program has included support of epidemiologic studies in the Northeastern Mid-Atlantic Region of the U.S. on the effects of dichlorodiphenyltrichloroethane (DDT) and polychlorinated biphenyls (PCBs) on breast cancer risk; support of the Long Island Breast Cancer Study, which focuses on risk from DDT and PCBs, polyaromatic hydrocarbons, and electromagnetic fields; and studies in North Carolina and California on organochlorine pesticides. In U.S. populations of women studied years after exposure has occurred, there doesn't seem to be a relationship between DDT exposure and breast cancer risk. Findings related to other environmental exposures are still to come. Currently we support six epidemiologic studies that look at patterns of breast cancer incidence, mortality, and survival rates to try to uncover additional clues about populations which are susceptible to breast cancer. NIEHS also supports mechanistic animal and clinical studies that are focusing on the effects of PCBs, organochlorines, and polyaromatic hydrocarbons on the expression of the BRCA1, breast cancer gene, kinases and other signaling pathways in breast cells, and on the cytochrome P450 (CYP) genes that may be involved in metabolism of pesticides and other xenoestrogens. The newly awarded Toxicogenomics Research Consortium supports experiments that will provide an understanding of the expression profiles of DNA repair and other genes that are involved in mammary carcinogens.

The Sister Study is a major new NIEHS initiative to study genetic and environmental risk factors for breast cancer in a cohort of 50,000 sisters of women who have had breast cancer. These asymptomatic women will be followed over time with periodic health updates. Those who do develop breast cancer, or other diseases, during the follow-up period will be compared with a sample of those who remained healthy to identify factors associated with increased cancer risk. The "cancer-free" sisters have about twice the risk of developing breast cancer themselves, presumably because they and their affected sisters share many of the same genes and early life exposures. We anticipate that after five years of follow-up, 1,500 women in the cohort will have developed cancer.

NIEHS is working towards expanding our support of research in this area and we are actively identifying exciting scientific opportunities and creating a research agenda in the area of breast cancer and the environment in partnership with the National Breast Cancer Coalition and other federal agencies. In the coming year NIEHS intends to provide significant leadership in this area by creating a new interdisciplinary research program with community involvement to study what causes breast cancer and how to prevent it.

DIABETES AND HEART DISEASE

Mrs. Lowey: Dr. Lenfant, the Department recently announced the findings of a study that shows that most Americans with diabetes do not appreciate their heightened risk for heart disease. What is NHLBI doing to help educate those with diabetes about this risk. Specifically, what are you doing to help prevent and treat heart disease for individuals with juvenile diabetes?

Dr. Lenfant: The NHLBI is directing educational messages to professionals, patients, and the public to make them aware that individuals with diabetes have an increased risk for coronary heart disease (CHD). Special emphasis is being placed on two major CHD risk factors–high blood cholesterol and high blood pressure. The new Adult Treatment Panel III (ATP III) clinical guidelines for cholesterol management summarize and emphasize the scientific evidence that an individual with diabetes has as high a risk for having a heart attack in the next 10 years as someone who already has CHD. Moreover, aggressive lowering of the LDL ("bad") cholesterol in persons with diabetes will greatly reduce their CHD risk. ATP III thus assigns to persons with diabetes the lowest LDL goal (LDL <100 milligrams per deciliter), and recommends aggressive treatment with lifestyle changes and drugs to achieve it. The ATP III conclusions and recommendations are being conveyed through a variety of approaches. Health professionals are being encouraged to treat individuals with diabetes aggressively and to help educate their patients about the benefits of doing so. The NHLBI has also conveyed the ATP III message to individuals with diabetes in several ways. The new patient brochure, "High Blood Cholesterol–What You Need to Know," stresses the high risk for CHD conferred by diabetes; it is available directly from the NHLBI Health Information Center and the NHLBI Web site, and is being distributed to patients by their physicians. The importance of cholesterol lowering in individuals with diabetes has been conveyed in the electronic kit of public education materials prepared for Cholesterol Month (September of each year). Detailed information about the risk for CHD in individuals with diabetes and how to lower cholesterol is also accessible to patients and the public on the NHLBI interactive Web site "Live Healthier, Live Longer." In addition, the ATP III emphasis on aggressive cholesterol lowering for people with diabetes is being communicated through the National Institute of Diabetes and Digestive and Kidney Diseases' ABC program (the "C" of which stands for cholesterol), which directs educational messages about lowering CHD risk to individuals with diabetes.

The NHLBI, through its National High Blood Pressure Education Program (NHBPEP), provides working group reports and guidelines to clinicians regarding the latest research findings. A recent clinical advisory on the treatment of hypertension and diabetes reinforces the importance of treating high blood pressure in patients with diabetes. It strongly recommends that antihypertensive therapy begin even before patients cross the traditional hypertension threshold of 140/90 mmHg, and indicates that ACE inhibitors have been shown to have unique benefits in preventing cardiovascular disease (CVD) and diabetic nephropathy. The NHBPEP is promoting community

awareness and action through its National High Blood Pressure Education Month activities, which includes a new Month Kit available on the NHLBI Web site. The Kit provides information for the public and patients regarding steps they can take to reduce their CVD risk by preventing and controlling high blood pressure. It also mobilizes organizations such as churches to take action by screening for high blood pressure and providing diet plans that are heart-healthy and lower the risk not only for CVD but for diabetes as well. The Kit is promoting educational messages to the public produced by the NHLBI's Healthbeat radio for the National Institute of Diabetes and Digestive and Kidney Diseases' National Diabetes Education Program. The messages encourage patients with diabetes to act because of their increased risk of CVD.

The NHLBI's new ATP III clinical guidelines for cholesterol management recommend that individuals with type 1 diabetes, formerly called juvenile diabetes, receive the same aggressive LDL-lowering treatment as those with type 2 diabetes because the former will have many decades of exposure to this potent risk factor for CHD. The NHLBI is also pursuing research on type 1 diabetes. One study is assessing the prevalence of clinical coronary artery disease in 800 individuals with insulin-dependent diabetes (aged 20- 49 years) and 600 nondiabetic spouse/partner controls. It is measuring coronary calcium, as an indicator of atherosclerosis, to assess the age at which significant coronary artery disease begins in individuals with type 1 diabetes. During 3 years of followup, investigators will identify the metabolic and behavioral risk factors associated with disease progression. In a second study, about 600 individuals from a cohort of persons with type 1 diabetes who were under 30 years of age when first identified in 1979-1980 are being contacted to measure a variety of CVD risk factors and document events such as heart attack, angina, congestive heart failure, stroke, and lower extremity disease, know as peripheral arterial disease. Results to date have shown that retinal microvascular abnormalities are predictors of stroke that are independent of blood pressure and other risk factors.

EDUCATING HEALTH CARE PROVIDERS AND THE GENERAL PUBLIC

Mrs. Lowey: Dr. Collins, as biomedical research advances, decisions based on genetics will confront more and more people. At the same time, most people are not familiar with genetics or even the terminology involved. What can the National Human Genome Research Institute (NHGRI) do to provide information about the Human Genome Project to health care providers and the general public?

Dr. Collins: Research on the human genome is running dramatically ahead of schedule, and will provide profound opportunities for better disease prevention and health promotion. With the tools provided by the Human Genome Project, the ability to identify hereditary susceptibility factors for common disease is advancing rapidly. This promising future of better prevention, treatment and cure will only happen if we are preparing health care professionals and the public for the coming revolution in genomic medicine.

To successfully prepare the public, those generating health care messages and answering public inquiries must have reliable information and remain closely aligned with the physicians and scientists conducting this research. NHGRI has taken a number of steps to achieve this objective. To provide accessible, validated information about genetics to primary health care providers, NHGRI founded the National Coalition for Health Professional Education in Genetics, in collaboration with the American Medical Association and the American Nurses Association. Over 100 professional organizations are now members of NCHPEG, which has recently enumerated a set of core competencies in genetics that all health professionals should have. Our current information products for the public include a free multimedia educational kit that has been requested by more than 60,000 individuals, many of them high school teachers, and that is now available on the web. Together with the Office of Rare Diseases, NHGRI has also established a Genetic and Rare Diseases Information Center. Since opening in January 2002, the Center has already handled many hundreds of complex inquiries.

The NHGRI has also held three Consumer Days, the most recent of which was held on November 9-11, 2001 in collaboration with the Zeta Phi Beta Sorority, the National Human Genome Center at Howard University and the Family Life Center Foundation of Shiloh Baptist Church. The program, which was open to all those interested in learning more about genetics and the NHGRI, explored issues such as Understanding the Basic Science of Genetics, Genomic Research on the African Diaspora, and Controlling Your Genetic Information. Finally the NHGRI has created Genetic Resources on the Web (GROW). GROW seeks to encourage communication and collaboration among individuals and organizations interested in web-based information on human genetics. The mission of GROW is to optimize web-based provision of high quality information about human genetics, especially information dealing with health. The NHGRI will continue to work to find new ways of explaining the complexity of genetics to the public and health care providers.

THALASSEMIA CLINICAL RESEARCH NETWORK

Ms. DeLauro: Dr. Lenfant, as you know, I have been a long-time supporter of the Cooley's Anemia Foundation and I am very grateful for your efforts in creating the Thalassemia Clinical Research Network. It is my understanding the material I have reviewed that the Network currently has two research projects underway and that they are reviewing additional projects. Could you share with the committee your assessment of the progress that has been made to date? What steps will your institute be taking to support further research being conducted through the Network?

Dr. Lenfant: The Thalassemia Clinical Research Network is in the early stages of addressing questions related to the bone disease associated with thalassemia and the treatment of hepatitis C. It is also undertaking a data collection project that will enable estimation of the prevalence of thalassemia and its complications in North America and determination of the availability of potential participants for Network studies. Although the Network has experienced some growing pains, we are now optimistic and confident that it will be successful, in part due to the very strong leadership of its Steering Committee.

The Institute has provided the basic infrastructure for the Network as well as statistical and programmatic resources. In addition to the studies of bone disease and hepatitis, a number of other protocols are currently under consideration, and the data collection effort mentioned above is expected to suggest directions for other clinical research studies. Moreover, complementary work supported by the NHLBI creates a large base of fundamental research and mechanisms of translation for phase I and II clinical trials. Studies are in progress that promise not only to ameliorate the disease with currently available therapies but also to provide a cure through the approaches of gene therapy and stem cell transplantation. In addition to investigator-initiated grants, the NHLBI is supporting research solicited via a Request for Applications (RFA) for the induction of hemoglobin F as part of its Gene-Based Strategic Plan for the Cure of Hemoglobinopathies; and, in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases, RFAs on The Biology of Iron Overload and New Approaches to Therapy. The Small Business Innovative Research (SBIR) program and the stem cell biology/cellular therapies program are also expected to yield promising new approaches to thalassemia treatment.

HEART DISEASE IN WOMEN

Ms. DeLauro: Dr. Lenfant, as a member of the Congressional Heart and Stroke Coalition, I am very concerned about heart attack, stroke and other cardiovascular diseases in women–the leading cause of death of American women. Cardiovascular diseases kill more than 512, 000 women each year–more than the next 9 causes of death combined. Cardiovascular diseases kill almost as many women as all forms of cancer. Heart attack, alone, kills more than 6 times as many women as breast cancer. Stroke, alone, kills 2.5 times as many women as breast cancer. Public Law 105-340, the

women's Health Research and Prevention Amendments on 1998, includes a section on heart attack, stroke and other cardiovascular diseases in women. In addition to encouraging more research, the law requires information and education programs on heart disease in women. Please describe for this Committee any new initiatives you have begun in this work area.

Dr. Lenfant: The NHLBI is vigilant in ensuring that all relevant research projects include women study participants. Moreover, it supports a number of studies focused specifically on diagnosis, treatment, and prevention of disease in women. During the time since Public Law 105-340 was enacted, the Institute initiated two major prevention trials in teenaged girls. The Girls Health Enrichment Multi-Site Studies (GEMS) is developing and testing interventions to prevent excessive weight gain in African American girls as they enter and proceed through puberty. The Trial of Activity in Adolescent Girls is testing a school-based intervention, with links to community programs, to prevent the decline of physical activity that typically occurs among adolescent girls.

In regard to information and education programs, the NHLBI Women's Heart Health Education Initiative (WHHEI) was launched in late March 2001 with a successful 2-day education strategy development workshop to develop a blueprint for a comprehensive women's heart health education action plan. The major recommendation made by workshop participants was clear and consistent: the NHLBI should "develop a national public awareness and outreach campaign to convey the message that heart disease is the #1 killer of American women and that it can be successfully prevented and treated." Based on the strong recommendation of the strategy development workshop participants, the initial effort of the WHHEI is development of a comprehensive public, patient, and professional awareness campaign to increase awareness about heart disease as the #1 killer of women, motivate women to take heart health seriously and engage in personal action to reduce risks, and improve clinical preventive care and treatment of heart disease among women. The campaign will focus on women 40–60 years of age. It will also seek to motivate health professionals to provide their women patients with clear messages about heart disease prevention and a high standard of care for the treatment and control of heart disease and its risk factors. The campaign will be an integral part of the heart-health agenda of the NHLBI which is focused on meeting the cardiovascular health objectives in the federal government's Healthy People 2010 initiative.

PREVENTION OF HIV INFECTION

Ms. DeLauro: Dr. Grady, currently prevention is still our most effective weapon against HIV infection, and NINR-supported research has already become a valuable resource that complements the missions of other agencies, such as the CDC. The AIDS crisis is far from over, and the complexities of combating the effects of this many-symptomed disease are challenging for all health disciplines. Can you tell us what nursing research is doing to prevent HIV infection and manage the symptoms of AIDS?

Dr. Grady: Let me start with examples of research to manage the symptoms of AIDS. The new, more powerful antiretroviral drugs against HIV, which significantly delay progression of the disease, can also have side effects, such as fatigue, dyspnea, undesirable weight change, and redistribution of fat. Researchers tested a 12-week, supervised exercise program on patients with AIDS. The exercise treatment group showed increased stamina on the treadmill and reduced fatigue. In addition, weight, body mass index, subcutaneous fat, and abdominal girth, were decreased when compared to controls. There was no significant change in CD4+ cell count, copies of plasma HIV-1 RNA, or dyspnea in either group. These findings indicate that aerobic exercise training is safe for HIV patients and decreases many of the undesirable side effects of those on antiretroviral therapy.

Adherence to HIV therapy is another issue under study. Researchers explored the beliefs of 322 African-American women and their experiences with AZT therapy during pregnancy, and what they thought they were told by their health care professionals and peers. The women were mostly single, with a mean age of 32 years, and with incomes under $10,000. Findings indicate that although 81% had been told to take AZT therapy, only 70% did so. Almost three-fourths were told that AZT therapy would reduce transmission of AIDS to their child. A small group said nothing would make them take AZT therapy, and almost 20% believed their healthcare provider would not want them to take it. In sum, most women had good information and used the therapy, but there were a significant number who were uninformed, indicating a need for better communication and frequent clarification of the patients' perceptions.

NINR research on prevention of HIV infection has included a study that you alluded to in connection with the Centers for Disease Control and Prevention (CDC). This study was successful in recruiting and retaining hard to reach inner city African American and Latino adolescent minorities. Several tested interventions reduced HIV sexual risk behaviors significantly, including increased condom use, reduced frequency of sex, a lower number of sexual partners, and a reduction in sexually transmitted diseases. The researcher's interventions have been so successful that her curricula were selected by the Centers for Disease Control and Prevention as model curricula and are being disseminated internationally. Prevention studies by other investigators include: designing a culturally sensitive intervention for inner-city Chicago Latino adolescents; an intervention focused on preventing HIV transmission among recent immigrant Mexican Americans; a school-based intervention directed at Latina and African-American teens; and a community-based intervention for Pacific Islander teens.

HIGH BLOOD PRESSURE IN AFRICAN AMERICANS

Mr. Jackson: I am very concerned that the prevalence of high blood pressure in African Americans in the United States is among the highest in the world. As I understand it compared with whites, African Americans develop high blood pressure earlier in life and their average blood pressures are much higher. Since high blood pressure is a major risk factor for heart disease and stroke if comparisons are made to the white population, African Americans have a 1.3 times greater rate of nonfatal stroke if comparisons are made to the white population , a 1.8 times greater rate of fatal stroke and a 1.5 times greater rate of heart disease death. Dr. Lenfant, please tell the Subcommittee what the National Heart, Lung, and Blood Institute is doing to address these health disparities in African Americans?

Dr. Lenfant: The NHLBI uses a variety of approaches to address the disproportionate burden of hypertension among African Americans. They include basic research on the biological origins of high blood pressure, identification of environmental contributors to the disease in various populations within the United States with the intention of developing more effective preventive and treatment approaches, and development of evidence-based clinical strategies to enhance the therapeutic options for different subpopulations of hypertensive individuals.

With regard to basic research, investigators have been studying gene variations that may contribute to the higher levels of hypertension in African Americans. Genes involved in the regulation of salt metabolism by the kidney are now believed to represent major contributions to high blood pressure in African Americans. A longitudinal study on children and adolescents has shown that the pathophysiology of hypertension begins during the teenage years and that young African Americans tend to display more rapid increases in blood pressure with age than do Caucasian children. Also noted is that differences in levels of various hormones early in life may cause African Americans to be more susceptible to developing hypertension later in life.

The Institute continually monitors trends in the prevalence and health impact of hypertension in African Americans with the objective of assessing progress in reducing health disparities. Measures of hypertension and its consequences are included in many of the Institute's population-based studies and clinical trials. Progress in awareness, treatment, and control is monitored and risk factors for lack of awareness and inadequate treatment are identified to assist in intervention efforts at the community and practitioner level. Extensive investigation continues into the causes of hypertension and its health consequences in African Americans, including the role of diet, obesity, genetics, stress, lifestyle, and socioeconomic status.

The NHLBI has also made a large investment in research aimed at evaluating interventions for prevention and treatment of hypertension, with an emphasis on obtaining results that are applicable to African Americans. Dietary and lifestyle interventions have demonstrated that modest weight loss and a reduction in sodium

intake can lower the incidence and severity of high blood pressure. In addition, a large NHLBI-funded clinical study is assessing the most effective pharmacologic treatment for hypertension in African Americans.

This body of basic and clinical research is providing the foundation for the extensive efforts of the Institute's National High Blood Pressure Education Program (NHBPEP), whose activities are aimed at improving prevention and treatment of high blood pressure. African Americans are a special target group for the NHBPEP's outreach programs. Since its inception, the NHBPEP has been informing African Americans about the dangers of high blood pressure and encouraging them to have their blood pressure measured and to seek treatment for hypertension. Activities to disseminate these messages include: media efforts on the HealthBeat Radio Network; the development and distribution of church guides as a planning tool to develop high blood pressure screening and tracking programs; a blood pressure planning kit for young men that is distributed at sporting events; the development of local coalitions among major academic centers in the southeastern section of the country to create education programs for stroke prevention; and the production of educational pamphlets dealing with the use of low-salt and low-fat cooking ingredients in African American recipes.

REDUCING HEALTH DISPARITIES

Mr. Jackson: NINR has prominent in research involving various ethnic and cultural populations. Could you give us more information about what NINR is doing to even the playing field for minorities and reduce the wide health disparities in our country?

Dr. Grady: Reducing healthcare disparities is a major goal of nursing research. Ethnic and cultural factors have a major influence on health and illness and will continue to be a special focus of nursing research. Here are some examples of what we are doing:

Clearly, a normal birth is an important first step to a healthy lifestyle. Yet according to the National Center for Health Statistics, the United States is a disappointing 26th among industrialized nations in the number of babies per 1,000 dying before their first birthday. Let me describe one of the ways nursing research addresses this issue. Nurse investigators targeted low-income pregnant African American and Caucasian women at particular risk for low birthweight. Registered nurses made home visits and followed up with low-cost, low-tech local phone calls to interact with the women on a regular basis. Results indicate the low birthweight rate was 10.9 percent compared to 14.0 percent for controls. For African Americans 19 years of age and older, the results were 11 percent versus 17 percent. Cost savings to the hospital were $277 per pregnancy. The research intervention was expanded to include Hispanics, and the intervention concept is now in use in four programs being operated and funded by private sector organizations, including a national HMO.

Another example would be the conversion of a successful arthritis self-management program from English into Spanish. Researchers observed that Hispanics with arthritis did not have many resources available to them about how to live with their condition and manage its symptoms. Furthermore, most measurement scales used were only in English. The investigators adapted and translated the scales into Spanish, and tested their efficacy in measuring pain for Spanish speakers of different national origins and regions. A year after the self-management course was completed, participants showed significant improvement in range of motion exercise, degree of disability, relief of pain, and self confidence. The Arthritis Foundation is working to foster adoption of this intervention nationwide.

NURSING RESEARCH ON HARD-TO-REACH POPULATIONS

Mr. Jackson: Your remarks today illustrate the impact of nurses at the community level, particularly in interacting with hard-to-reach populations, such as older people, certain members of minority groups, and rural residents. Could you summarize studies your institute supports to reach these populations?

Dr. Grady: NINR research findings indicate that high blood pressure in young, inner-city African American men, a major health risk for this hard-to-reach population, can be reduced significantly. Through an intervention that included hypertension education, referrals to medical care, and community health care, the number of men after 3 years with controlled blood pressure rose from 17 percent to 44 percent, well above the national rate of 27 percent.

Researchers have tested a transitional care model on older people hospitalized with common medical and surgical problems. The problems represented the top ten categories in Medicare reimbursement. The model involves advanced practice nurses who conduct comprehensive hospital discharge planning, including determining the patient's care needs outside the hospital, with follow-up in the home. Findings indicate that the number of days in the hospital was reduced by 65 percent, and rehospitalizaitons and costs to the healthcare system were reduced by 48 percent for these patients. Investigators are now testing this model on patients in rural settings.

A recently funded study involves computer-based education for 300 rural, primary school children with asthma. Computers appeal to children and require minimal staff time. Children can learn ways to better manage their asthma, including controlling common environmental triggers, such as bedroom allergens. The intervention will be assessed to determine possible improvements in the children's health and quality of life.

MALT LIQUOR

Mr. Jackson: What is the NIAAA doing to examine the public health and community impacts of high alcohol content malt beverages, which are aggressively marketed to inner-city ethnic populations and young people?

Dr. Kington: We are actively pursuing this issue. In 2000, a NIAAA-sponsored working group of scientists found that there were few data on the impact of malt and wine specialty beverages on health and social problems in racially, ethnically, and economically diverse communities. We subsequently published a Request for Applications (RFA) on this topic the following year. This RFA resulted in funding of eight exploratory/developmental grants in 2001, and these studies are ongoing. The grantees met in 2002 to assess progress and to share information, and are scheduled to convene again in 2003.

LIQUOR-BRANDED MALT BEVERAGES

Mr. Jackson: Has the NIAAA studied the marketing and consumption of the new crop of heavily advertised, youth-oriented liquor-branded malt beverages, such as Smirnoff Ice, Bacardi Silver, Captain Morgan Gold, Skyy Blue, etc.?

Dr. Kington: NIAAA recognizes that new alternative malt beverages with various contents are rapidly entering the market. Many of these products entered the market after we awarded eight grants, in 2001, to study the impact of malt and wine specialty beverages on health and social problems in racially, ethnically, and economically diverse communities. We will make every attempt to incorporate these new products in our malt-beverage studies, and we agree that research on marketing and consumption of this new breed of malt beverages is warranted.

DIABETIC RETINOPATHY

Mr. Jackson: Diabetic retinopathy is the leading cause of new cases of blindness in working age adults. We know that laser treatments have been successful in delaying the onset of blindness in individuals with diabetes, but it has not solved the problem. In fiscal year 2002, the committee's report encouraged NEI to discover ways to control the proliferation of abnormal vessels that give rise to diabetic complications within the eye and on other organs and systems of the body. What has been the progress of this research? What is the most promising avenue of research to develop methods to prevent sight-threatening damage in individuals with diabetes?

Dr. Sieving: The abnormal growth or proliferation of blood vessels is a process known as neovascularization. A number of diseases involve neovascularization, including the growth of some tumors, arthritis, and a variety of eye diseases, including diabetic retinopathy. In the eye, neovascularization can have a devastating impact on vision. Research has indicated that certain proteins involved in growth of blood vessels are elevated in patients with abnormal blood vessels and that one growth factor, vascular endothelial growth factor (VEGF), is consistently elevated in these patients. Studies have suggested that in diabetic retinopathy, blockage of the blood vessels in the retina produces a lack of oxygen that stimulates VEGF production. Several proteins or drugs have been found to inhibit or stimulate the neovascular process, including those that inhibit VEGF, and are currently being evaluated for their therapeutic potential.

In individuals with diabetes, the most devastating threat to sight occurs in proliferative diabetic retinopathy. The rapid growth of abnormal new blood vessels can lead to the sight threatening leakage of fluids and proteins into the retina and ultimately to hemorrhage of damaged vessels and vision loss. Among the most promising avenues of research are those exploring ways to inhibit the growth of new vessels. Many of the compounds being evaluated are also under evaluation for cancer treatment. One such promising protein is endostatin, a potent inhibitor of blood vessel growth (angiogenesis) in tumors. In order test the effects of endostatin on ocular neovascularization, NEI-sponsored researchers developed a viral vector to transfer the gene sequence for endostatin into an animal model of neovascularization. These scientists found that the endostatin gene transfer successfully sustained high levels of endostatin that prevented choroidal neovascularization in the model.

Another compound under investigation is known as PKC 412, which can be taken orally and blocks new vessel growth without having adverse effects on normal, mature vessels. The uniquely specialized tissues of the eye make it especially difficult to predict the full therapeutic potential that a promising protein or drug might have on the neovascular process, but continuation of this research will ensure that the most promising ones are thoroughly evaluated for safety and efficacy in clinical trials at the earliest possible date.

CLEFT LIP/CLEFT PALATE

Mr. Kennedy: We have heard a lot about the advances made in genetics at NIH. I understand that the condition cleft lip/cleft palate is one of the most common birth defects of children. What has your research shown about this defect and can you offer any hope for preventing it in the future?

Dr. Tabak: Our research shows that most cases of cleft lip/cleft palate cannot be pinpointed to changes in a single gene or protein product, as was once hoped to be the case. As with so many human developmental anomalies, the story is far more complex, involving multiple genes and their interplay with myriad environmental factors. Though scientists are still in the initial stages of identifying the biological and environmental factors involved in the process, there is good reason to hope that improved prevention strategies will emerge.

One reason for this hope is that several significant advances in identifying the genetic basis for non-syndromic cleft lip/cleft palate have been made by NIDCR-supported scientists, and recent studies have considerably expanded the list of genes known to be involved in oral clefting. For example, it was a NIDCR-supported team that identified "PVRL1" as the gene responsible for a rare recessive clefting syndrome associated with ectodermal dysplasia, a disorder that includes defects in the skin, teeth and hands as well as clefting, and occurs in a high frequency among the population of Margarita Island in the Caribbean Sea. More recently, this research team has provided preliminary evidence that individuals carrying only one copy of the mutated gene exhibit an increased risk for cleft lip/cleft palate that is not associated with the other defects of the syndrome. In addition, a NIDCR-supported researcher and his team demonstrated that the "SKI" cancer gene plays a role in the risk of clefting. At the May 2002 meeting of the American Cleft Palate-Craniofacial Association, a NIDCR-supported researcher reported on the identification of a new gene, interferon regulatory factor 6, that has a major impact on van der Woude syndrome, the most common syndrome involving orofacial clefting. Further studies will focus on whether this gene also has effects on non-syndromic forms of clefting.

The NIDCR is now in the third year of support for a five-year project with the World Health Organization for planning, protocol development and database development for international collaborative biomedical, epidemiological and behavioral research in the area of craniofacial birth defects, including cleft lip and palate. The goal of this initiative is to bring together international orofacial cleft researchers through collaborative partnerships, and to develop global consensus on craniofacial birth defect research directions and common research protocols. International consensus conferences have been held in the areas of genetics, gene-environment interactions, epidemiology, treatment and prevention of clefting, and a WHO report of these conferences is due to be published later this year. This initiative also includes efforts to develop and give researchers access to a central global craniofacial birth defects registry.

Regarding research directions that are examining non-genetic factors, studies indicate that specific environmental exposures during pregnancy, such as maternal tobacco and alcohol use, increase the risk of craniofacial birth defects. Evidence that maternal periconceptual deficiencies in vitamin B6, folic acid and other micronutrients may be associated with an increased risk of cleft lip/cleft palate has given direction for possible future intervention research.

ORAL HEALTH AND LOW-BIRTH WEIGHT BABIES

Mr. Kennedy: We have heard that there is a connection between a birth mother's oral health and low-birth weight babies. For the record, would you explain the research being done on that potential association? Do you know what the link is between the two?

Dr. Tabak: Pre-term birth and low-birth weight are considered the leading perinatal problems in the United States. NIDCR-supported investigators have been at the forefront in demonstrating potential associations between periodontal disease and these perinatal problems. Recent studies indicate that a woman may be 3 to 8-fold more likely to deliver a pre-term low-birth weight baby if she has moderate to severe periodontal disease. In one NIDCR-funded study, investigators have found that pregnant women who fail to mount a strong antibody response against the microorganisms that are implicated in periodontal disease are at a significantly higher risk for premature delivery. This is consistent with the concept that maternal antibody has a protective effect and favors full-term delivery. In another NIDCR-funded study, a clinical trial is being conducted to determine if treating periodontal disease will lower the risk of delivering pre-term low-birth weight babies. The results of this trial demonstrate that treatment by simply cleaning the teeth significantly reduces the incidence of pre-term births. Of major interest, however, is the finding that somewhat more extensive treatment, scaling and root planing, dramatically reduces pre-term births. If this finding proves true to the general population, a simple intervention of scaling and root planing teeth may be used to reduce the numbers of premature babies born in this country.

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