

**DEPARTMENTS OF LABOR, HEALTH AND
HUMAN SERVICES, EDUCATION, AND RE-
LATED AGENCIES APPROPRIATIONS FOR
FISCAL YEAR 2008**

MONDAY, MARCH 26, 2007

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

The subcommittee met at 3:30 p.m., in room SD-116, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.
Present: Senators Harkin and Specter.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

**STATEMENT OF HON. THOMAS R. INSEL, M.D., DIRECTOR, NATIONAL
INSTITUTE OF MENTAL HEALTH**

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. The Appropriations Subcommittee on Labor, Health and Human Services, and Education and Related Agencies will come to order. This is the subcommittee's second hearing on the National Institutes of Health this year. Last week we heard from NIH Director Elias Zerhouni and several top extramural scientists as we discussed the need for more NIH funding. Starting today and over the course of the subcommittee's next five NIH hearings, we will hear from each of the Institute and center Directors, usually in groups of four or five.

We had actually done this before. I like this room, I like the setting, I like the way that we are at a table here, which makes it more conversational, rather than just sitting at a podium, that type of thing. So I like this much better. This is one of our Appropriations rooms. In fact, our predecessor on this when I first came to this committee used this room and we had those hearings at that time. I like the idea. I like the setting of it, so I am going to try to use this room as often as possible for these kinds of hearings. It is not as formal, it is more relaxed, and we can have a conversation.

I will ask each of the Directors to speak for about 5 minutes. We have your statements. We will make them a part of the record in their entirety. So I am just going to ask you for about 5 minutes to talk about some of the most important functions that you see in what you are doing, and then we will have a discussion with you,

and we will do each Director's time. So I am thinking about 15 minutes per person, and we will do it that way. Then at the end, maybe if there are some wrap-up things, then we will just kind of open it for a general thing at that time.

So the five Institutes that are here today—NIMH, Mental Health; National Institute on Drug Abuse, NIDA; the National Institute on Alcohol Abuse and Alcoholism, otherwise known as NIAAA; National Institute on Deafness and Communication Disorders; and the National Institute of Neurological Disorders and Stroke, Dr. Landis. We grouped these together because all of these have to do with mind-brain behavior, and I am going to try to continue this kind of lumping together of different Institutes as we have these hearings.

However, I just say that if you have other things you want to bring up, please do. Anything happening in your Institutes is fair game for us to discuss.

With that, I turn to Senator Specter if you have anything in opening.

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Thank you, Mr. Chairman.

We continue our hearings on the National Institutes of Health, and I consider this to be a matter of priority second to none in our budget. Health is our principal capital asset and the work which has been done by NIH has been truly spectacular. Senator Harkin and I have taken the lead, as is fairly well known, in increasing the funding for NIH from \$12 billion to almost \$30 billion, and we have done that by taking a very sharp pencil and establishing priorities and eliminating items from a very important budget in deference to the greater importance of health care.

We have three major Departments that we are responsible for funding: Health and Human Services, Education, and Labor. So that we have had to evaluate education priorities and worker safety priorities and health care priorities. But NIH has the potential to be a fountain of youth, in my opinion, and to really find ways to fund cures for many, many ailments.

I say with some frequency, but not often enough, that when President Nixon declared war on cancer in 1970—had that war been pursued with the same intensity as other wars—my chief of staff, a beautiful young woman named Carie Lackman, at 48 would not have died of breast cancer, and last year one of my best friends, the Chief Judge of the Third Circuit emeritus, would not have died of prostate cancer; and I would not have gotten Hodgkins.

When we talk about containing costs, the best way to contain costs is to prevent disease and to prevent illness. Senator Harkin and I are leading the fight for embryonic stem cells. It is scandalous when you have the major responsibility for funding health programs in the Federal Government but are not able to use any funds for stem cell research. Now, if these embryos would produce children we would be the last to suggest they be used. But we have taken the lead in putting up \$2 million to have adoptions, but only about 100 of some 400,000 have been adopted. So it is a matter of using them to save lives or having them ultimately discarded.

Senator Harkin and I added an amendment to the budget resolution last week for \$2.2 billion and that is only to stay afloat and tread water from the cost of living adjustments. But do not draw too much encouragement from it because the budget resolution is only Confederate money. The money does not materialize until there is an allocation. Then it does not materialize until there is an appropriation, and to call it Confederate money may be giving it too much credit. It may be more accurately called Monopoly money.

But we are determined to fight this through. You can help us. As we said to Dr. Zerhouni last week, we need to have the best estimates you can make as to what this research means in terms of saving lives and quantifying—I know it is hard to do—how long it will take to find a cure for a given malady and how much it will save. For example—if you delay the onset of Alzheimer’s—I have seen some statistics that shows health care cost savings into the billions of dollars. But that is what motivates the other 535 Members of Congress, if you can be specific and show them some savings.

So thank you for what you are doing and I look forward to your testimony.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Specter.

So we will start with Dr. Insel, then Dr. Volkow, Dr. Battey, and then Dr. Landis.

Dr. Thomas Insel has been the Director of the National Institute of Mental Health since September 2002, received his B.A. and M.D. degrees both from Boston University. So Dr. Insel, welcome. As I said, your statement is part of the record. Tell us what you are doing, what is important, and what we ought to know about.

SUMMARY STATEMENT OF DR. THOMAS R. INSEL

Dr. INSEL. Thank you. First of all, Mr. Chairman, let me say how much we all appreciate being here. I have been in my job now for about 4½ years. I think this is the first time I have had a chance to talk with this subcommittee and update you with the kinds of things we are interested in.

At the beginning, I would like to just very quickly run through where we see the biggest needs and then tell you a little bit about what we hope to do about them. There is no question that the needs across all of these Institutes in terms of the public health burden is very great. You will be hearing from all five of these NIH Institutes that focus on neuroscience and behavior. Together we cover about 1,000 disorders of the nervous system affecting about 70 million Americans. These result in more hospitalizations than any other class of illnesses, including cancer and heart disease. You will hear about some of the costs, which in aggregate are about \$800 billion per year. For my Institute, the mental health piece of this alone, represents for all health care about 6.2 percent of the overall cost, and some parts of that are going up, such as medications, at a rate of about 20 percent per year.

PREPARED STATEMENT

I think you know that the health care costs have now become about 16 percent of the GDP, predicted to go up to 20 percent by 2016. So these are very significant costs in the entire economy.

[The statement follows:]

PREPARED STATEMENT OF DR. THOMAS R. INSEL

Mr. Chairman, and members of the Committee: I am pleased to present the fiscal year 2008 President's budget request for the National Institute of Mental Health (NIMH). The fiscal year 2008 budget includes \$1,405,421,000. In my statement, I will call to your attention our Nation's most prevalent mental and behavioral disorders and include a brief review of our research activities and accomplishments.

MENTAL DISORDERS ARE CHRONIC BRAIN DISORDERS

The NIMH mission is to reduce the burden of mental and behavioral disorders, such as depression, schizophrenia, autism, and bipolar disorder, through research on mind, brain, and behavior. Research is demonstrating that these illnesses are brain disorders, accessible by the tools of modern neuroscience. These disorders frequently begin in childhood and are chronic,¹ affecting people of all races and ethnicities, in both rural and urban settings. To prevent a lifetime of disability for millions of Americans, NIMH research is identifying the biological basis of mental disorders, and pinpointing targets for diagnosis, prevention, and treatment.

PUBLIC HEALTH BURDEN OF MENTAL ILLNESS

In the most recent national household survey, as many as 44 million Americans met criteria for some mental disorder, with roughly 12 million reporting symptoms so severe as to cause significant disability in the past year.² According to the World Health Organization, mental disorders are also the leading cause of medical disability in the United States and Canada for people ages 15–44. The annual economic cost of mental illness in the U.S. is estimated at well over \$150 billion, with most due to the indirect costs of social services.³ The direct costs of mental health care represent 6.2 percent of the overall health care costs,⁴ which totaled 14.5 percent of the gross domestic product in 2001 according to the Centers for Medicare and Medicaid Services (CMS).

ADVANCING CLINICAL RESEARCH IN MENTAL HEALTH

New tools in genomics, imaging, and behavioral science have given us traction for progress towards reducing this tremendous public health burden. NIMH has adopted the NIH clinical research vision, which focuses on the four *P*'s of medical research: increasing the capacity to *Predict* who is at risk for developing disease; developing interventions that *Pre-empt* the disease process; using knowledge about individual biological, environmental, and social factors to *Personalize* interventions; and, ensuring that clinical research involves *Participation* from the diversity of people and settings affected.

The Institute's focus on practical, or "effectiveness," clinical trials embodies this research vision. Although traditional clinical trials are useful in determining if groups of patients respond to a treatment, NIMH's practical clinical trials, conducted with 10,000 patients at 200 sites across the nation, have helped us to understand individual responses to treatment. DNA collected from participants in one such trial, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), led to the discovery of genetic variations associated with response to antidepressants. Through the inclusion of a diverse population, this research also found that the genetic variation that predicted a favorable response was less com-

¹ Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*. 2005 Jun;62(6):593–602.

² Kessler, RC, Chiu, WT, Demler, O, Merikangas, KR, Walters, EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*. 2005 Jun: 62, 617–627.

³ New Freedom Commission on Mental Health, *Achieving the Promise: Transforming Mental Health Care in America*. Final Report. DHHS Pub. No. SMA-03-3832. Rockville, MD: 2003.

⁴ Mark TL, Coffey RM, Vandivort-Warren R, Harwood HJ, King EC; MHSA Spending Estimates Team. United States spending for mental health and substance abuse treatment, 1991–2001. *Health Affairs (Millwood)*. 2005 Jan-Jun;Suppl Web Exclusives:W5-133-W5-142.

monly found in African-Americans. This pharmacogenomic approach can transform the treatment of mental disorders, allowing clinicians to personalize therapy choices based on a patient's unique biology.

Results from these practical trials and related studies have taught us that current medications are helpful but not sufficient for most people with schizophrenia, depression, and bipolar disorder. While research on non-drug therapies is showing impressive results in treating a variety of mental illnesses, we clearly need a new generation of medications that are more effective and better tolerated. NIMH research during the past year reported on new classes of antidepressants that work within hours rather than weeks. These findings suggest that we can expect new medications that will transform the treatment of mental illnesses by influencing recently discovered targets in the brain.

New treatments like these antidepressants are based on the emerging science of pathophysiology, the study of how brain structure and functioning are involved in mental disorders. For instance, research on fear has revealed a class of brain receptors and specific brain circuits involved in traumatic memories. Clinical trials with medications that specifically target those receptors and circuits have shown positive effects in reducing stress in response to reminders of trauma and, thereby, offer a new treatment for PTSD. Working with the Department of Defense and the Department of Veterans Affairs, NIMH is supporting research that will treat PTSD and may also prevent the persistence of fearful memories, thus pre-empting the development of PTSD altogether. With 13 percent of returning soldiers diagnosed with PTSD,⁵ we recognize the urgent need for safe and effective pre-emptive interventions.

PARTNERSHIPS FOR RESEARCH PROGRESS

NIMH also aims to accelerate research discoveries through collaborative partnerships. Fifteen NIH Institutes invested in research on the nervous system have pooled resources to create the NIH Blueprint for Neuroscience Research, a framework to enhance collaboration in the development of research tools, resources, and training, all of which will be made available to the neuroscience research community. Initiatives will focus on neurodegeneration in 2007, neural development in 2008, and neural plasticity in 2009.

Through public-private partnerships and additional grants coordinated by the Foundation for the National Institutes of Health (FNIH), the Genetic Association Information Network (GAIN) program will investigate the genetic roots of several common diseases and to provide the immediate, broad release of scientific information through a publicly accessible database. Four of the six current GAIN initiatives are related to brain disorders: attention deficit/hyperactivity disorder, schizophrenia, bipolar disorder, and major depressive disorder.

The Biomarkers Consortium is a public-private research partnership of the FNIH that includes NIH, CMS, the Food and Drug Administration, and industry and advocacy organizations to help identify new and valid biomarkers that will advance the creation of innovative technologies and therapies for early detection, diagnosis, and treatment of disease. Some of the first research findings from the Biomarkers consortium and GAIN are expected later in 2007.

These joint initiatives offer translational opportunities for further developing interventions and treatment options that can deliver more effective, personalized care across diverse populations and settings.

In summary, this is a time of unprecedented excitement in mental health research. Neuroscience and genomics are yielding new insights and new treatments, providing great hope for the future. Large-scale, practical trials are helping us optimize the treatments available today. I appreciate this opportunity to tell you about those exciting breakthroughs in the science of mental illness. I look forward to your questions.

INDIRECT COSTS OF MENTAL ILLNESSES

Senator HARKIN. You are saying that mental health is 6.2 percent overall? It is not—

Dr. INSEL. It is 6.2 percent of the overall costs of health care.

Senator HARKIN. Of the 16 percent.

⁵Seal KH, Bertenthal D, Miner CR, Sen S, Marmar C. Bringing the War Back Home: Mental Health Disorders Among 103,788 U.S. Veterans Returning From Iraq and Afghanistan Seen at Department of Veterans Affairs Facilities. *Archives of Internal Medicine*. 2007 Mar 12;167(5):476-482.

Dr. INSEL. Of the 16 percent, right, of the GDP.

Now, you have to recognize that when I talk about the costs of health care for mental illness, that is telling you a very small part of the story. Many of the costs here are not in the health care system per se, but in the social services, what we call the indirect costs of these disorders. According to the President's New Freedom Commission, which was a report issued in 2003, people with mental illness are the largest single group of patients in our public assistance programs, like SSI and SSDI. They are a large part of our homeless population and, according to the Department of Justice program on statistics there, our prisons and jails have increasingly become really the institutions for those with chronic mental illness, at least half of the people incarcerated having a serious mental illness, which is just extraordinary.

Now, how you capture those costs is quite difficult. None of them are captured when we talk about the costs of health care. At the very least, I think it is fair to say that these indirect costs of mental health care swamp whatever it is that we are paying in the direct costs of providing medical care to those with mental illnesses. As you will hear, this is also true for addiction and alcoholism.

CHRONIC DISEASE

It is probably equally important for you to realize that the real costs are not just in dollars, but in lives lost. As Senator Specter was saying, this is really a question of saving lives. You probably heard from Dr. Zerhouni that we are now thinking of the 21st century as the era of chronic disease, and that is undoubtedly true. Diabetes, hypertension, and heart disease are all chronic diseases which will become the big challenge of this century.

But as you will hear from Dr. Volkow and others, mental and addictive disorders, are also chronic diseases. What sets them apart is they begin early in life. In a recent study, 50 percent of adults with mental illness reported onset by age 14, 75 percent by age 24.

What that really means is that these are in fact the chronic disorders of young people in this country, mental illness and addictive disorders. They start early. Many are chronically disabling. This is why the World Health Organization, when it was looking at the largest sources of medical disability, ranked these disorders—mental illness and addiction—the number one cause of disability for Americans between 15 and 44. So it is an extraordinary saga that is largely untold. We often say that the costs in dollars and in lives are unacceptably large and largely unrecognized.

Finally, let me just say before I turn this over is that one of the aspects of this, of these disorders being recognized as brain disorders, is that the group of people who are here at the table are now very much all of one mind. We can work together and collaborate in a way that was not as obvious a decade ago. You can see that in a number of ways. Not only do we recognize that there is a lot of comorbidity—Parkinson's and depression, certainly PTSD and addiction, bipolar illness and alcohol abuse—but it is also in the tools that we need.

NEUROSCIENCE BLUEPRINT

So we have come together to form the Neuroscience Blueprint, which I believe Dr. Zerhouni may have mentioned. It is an attempt to collaborate and to develop resources and tools that will serve all these Institutes and will make a difference for people with brain disorders. We have also got the embodiment of this collaborative effort in a new facility, the Porter Neuroscience Building, under the NIH intramural program, which is a very exciting effort that I hope I can tell you more about during the question period.

So I am going to stop here so we have more time, but I do want to say how much we appreciate the opportunity to be here.

DRUGS AND MENTAL HEALTH

Senator HARKIN. Dr. Insel, thank you very much.

Let me just lead this off. First of all, just a general question. On mental health, are we putting too many eggs in the basket of finding a drug that masks, that perhaps gets someone through a tough time to respond to the immediacy of a mental illness? Are we putting too much in just finding these kind of drugs rather than getting to the underlying cause and taking the time and research to understand what led to that point?

I say that because it just seems to me that more and more people with mental illness are just taking more and more drugs. I will tell you of a case I know vaguely, someone I happen to know. I do not want to get too specific because I want to protect privacy. Someone who is on a drug that was—I wish I could remember the name. I came here equipped to ask you about it. But it was a powerful antidepressant type drug. When that person decided to get off that drug, it was like getting off of heroin or something. The bodily reactions and the mental reactions of that person getting off that drug was just awful. I wondered, why would a doctor prescribe this in the first place?

So again, general question: Are we putting too much into just going after drugs or should we be looking at some of the underlying causes?

Dr. INSEL. The quick answer is yes. Let me explain that. This field in some ways has been cursed by having medications that are pretty good. These were not designed rationally. They were all discovered by serendipity. But surprisingly, some of them actually helped quite a few people. The down side is that much of the field of research has really focused on trying to improve the existing drugs instead of trying to understand the basic pathophysiology of the disorders. Understanding that would allow us to know how to design medications that really go after the core lesion, the core problem here. It also gives us some hints about how to get into preemptive care, how to get there before the psychotic part of schizophrenia emerges. We know schizophrenia is an illness that has many phases, just like heart disease. But we tend to intervene with heart disease before a myocardial infarction. We do not wait for someone to have a heart attack.

In this field, we are waiting for someone to have a psychotic break before we really intervene. We do not need to do that.

EATING DISORDERS

Senator HARKIN. You and I discussed this once before, but I was told—I am going to repeat this without knowing whether it is factual or not, but I was told on more than one time or occasion that what I am about to say is true: that the single largest cause of young women dropping out of college is eating disorders. A lot of this has to do with mental health problems.

So what is happening here? What is the Institute doing on this? Are you looking into eating disorders and the underlying mental health problems that either lead to it or exacerbate it?

Dr. INSEL. This is one of the places where, in contrast to what I just said about having pretty good medications that work for most people, we actually do not have medications that work for most people with eating disorders, nor do we have very rapid effective targeted psychotherapies or psychosocial therapies. This is one of the areas where we have the greatest difficulty with treatment.

Dr. Volkow and I have talked a lot about this and in some ways eating disorders resemble an addictive disorder, where a lot of women diet, only a few get hooked and start dieting to the point where they actually become—it becomes a life-threatening problem. We do not know how to treat that in a quickly targeted way, effectively, as well as we do many other disorders.

We also do not know how to predict who is at risk, and that is one of the biggest questions for us. What we would like to do is not come up with necessarily the optimal treatment after somebody is already down to 65 or 70 percent of their normal body weight. We would like to be able to find out how do you keep them from getting to that point by intervening very early in the process, perhaps before this kind of addictive component gets started.

EPIGENETICS

Senator HARKIN. The last question before I turn it over to Senator Specter. You are expanding a program called Human Genetics, Epigenetics, and Genomics Underlying Mental Disorders. I know what genetics means, I think I know what genomics means, but I do not know what epigenetics is. What is that?

Dr. INSEL. It is a new and exciting area which several people at this table care a lot about. In a word or in a sentence, genetics and genomics have to do with the sequence of the genome, so what is the text. Epigenetics are those things that modify the text. Think of it as a highlighting pen that causes certain parts of the genome to be expressed in a certain cell. In any given cell, only about 20 percent of your genes get expressed. Now, why is that?

Now, we partially know there are things that lay on top of the sequence. In some cases they reduce expression, in some cases they enhance it. That is the epigenetic tag or those are the modifiers to gene expression. We want to understand much more about how they work.

Senator HARKIN. Have you done much in that area in the past?

Dr. INSEL. Well, we have done quite a bit because we are interested in those parts—and we know that early experience does have something to do with whether you become addicted later, whether you develop depression or some of these illnesses. But we do not

have the tools yet to do this at the kind of high throughput, high resolution stage of what we can do with genomic sequence. So right in that area we are a little bit inhibited from being able to make the kind of progress we like. So the next step is going to be tool development.

Senator HARKIN. Senator Specter.

Senator SPECTER. Well, thank you, Mr. Chairman. If I may say so, I would prefer to hear what the witnesses have to say. I am going to have to excuse myself at about 4:30, and my preference, if it is acceptable to the chair, would be to hear them and then ask a question or two.

Senator HARKIN. Well, the only reason I wanted to do it this way is because then it is fresh on our minds. When he says something, I can interact with him. I thought we would go down each one. I would rather, if you do not mind, do it this way. But if you have to leave—and believe me, I understand everybody has got different schedules—if you have something for one of the directors, if you want to direct it, that would be fine.

Senator SPECTER. Okay. When it is more pressing than hearing them, I will do so. If that arises, I shall.

Senator HARKIN. No, but if you had something you wanted to ask someone now, if you have got to go, if you want to ask someone now, that would be fine.

Senator SPECTER. Well, let me hear Dr. Volkow. I do have one question which is very much on my mind, and there may be others. But let me defer to Dr. Volkow.

Senator HARKIN. Well, then next we will turn to Dr. Volkow, Director of the National Institute on Drug Abuse. Dr. Volkow received her B.A. from the Modern American School in Mexico City, Mexico, her M.D. from the National University of Mexico, Mexico City. Dr. Volkow, welcome. Please take 5 minutes and let us know what you are doing out there.

STATEMENT OF NORA D. VOLKOW, M.D., DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE

Dr. VOLKOW. Mr. Chairman, it is a privilege for me to be here with my colleagues to share some of our initiatives at the National Institute on Drug Abuse. As you know, the social and individual costs of substance abuse and addiction to the society are nothing less than staggering and utterly unacceptable. On economic costs alone, the Institute of Medicine estimated that substance abuse, legal and illegal, including nicotine and alcohol, costs this country over half a trillion dollars annually, which includes not only medical costs but costs associated with the criminal system.

NIDA's strategy to alter the course of this epidemic is based on a multi-pronged approach designed to understand how genes shape our brain, how environmental factors affect this process, and how brain function links to behavior, including that which characterizes addiction, which is the compulsive intake of the drug despite its catastrophic consequences.

From the science we have learned that repeated drug use affects the function of multiple systems in the brain, including those involved with reward and pleasure, which motivate our behaviors on a daily basis, systems involved with learning and memory, which

change our behavior as a function of experience, and systems involved with inhibitory control, which allow us to exert volitional control of our behaviors and emotions.

Today I will stress and highlight how stress, one of the key environmental factors influencing the vulnerability for addiction, affects brain development and how in turn that affects the propensity for taking drugs. We have learned that addiction is not just a result of chronic drug use, but that genetics and, as I say, environmental factors play an extraordinarily important role. However, because we can currently not change our genes, which actually account for 50 percent of the vulnerability to become addicted, a better understanding about how environment affects how our genes and brain develop offers an extraordinary opportunity for prevention.

It is particularly relevant because drug addiction is fully preventable even in those that have a genetic predisposition to become addicted, provided they do not get exposed to drugs. However, the challenge is how you interfere with young people's taking drugs. I say young people, and that is because drug experimentation basically starts in adolescence and the earlier you start taking drugs the greater the vulnerability to become addicted. Why is that so? Multiple factors.

One of them is that the brain when you are an adolescent is still in full development and many of the connections that link it with one another are not there. For example, the connections that associate your limbic brain, that is responsible for emotions and desires, with the thinking part of your brain, the prefrontal cortex, will not be fully formed until you are in your early 20s. As a result of that, adolescents are much more prone to engage in risky behaviors such as substance abuse.

Unfortunately, the consequences of environmental stressors that influence the vulnerability for drug abuse start as early as in utero. Now we know, for example, from studies in laboratory animals that early exposure during pregnancy of animals to marijuana leads to a dysfunction of the newborn that continues to adulthood.

Also, some very simple social stressors, such as we now know that if there is no physical contact between the newborn and the mother, physical contact, that will lead to silencing of a gene, what you were speaking about, epigenetics. That lack of physical contact silences a gene that is important in regulating our response to stress. These newborns then grow up to be very, very sensitive to stress, which is one of the factors that makes them vulnerable to addiction.

Unfortunately, we know too well that childhood exposure to social and environmental stressors are extremely deleterious. Indeed, our studies, for example, show that children that were exposed to five or more social stressors that include a parent in jail, a parent that takes drugs, physical sexual abuse, neglect, are 10 times, 10 times more likely to become addicted than those that are not.

Unfortunately, social stressors occur throughout all of our lives and at any age can lead to substance abuse, to the transition between substance abuse and addiction, and to relapse to those in recovery. Why? Because the systems that project stress have tremen-

dous overlap with the systems in the brain that project these drugs.

PREPARED STATEMENT

So in summary, we know, we recognize that drug addiction is a chronic disease that changes the brain in long-lasting ways, that profoundly affect behavior. We know that it is fully preventable, even in those that have a genetic vulnerability. Inasmuch as predisposition does not equate with predetermination, that knowledge about how environment affects our genes and our brain biology provides an extraordinary opportunity to tailor preventions to those that are at high risk because of their genetics or because of their environmental factors.

So thank you for your attention. I will be happy to answer any questions you may have.

[The statement follows:]

PREPARED STATEMENT OF DR. NORA D. VOLKOW

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2008 President's budget request for the National Institute on Drug Abuse (NIDA). The fiscal year 2008 budget included \$1,000,365,000. Today, I will discuss NIDA's multifaceted strategy to help reduce the enormous toll that drug abuse and addiction take on this Country, highlighting recent scientific accomplishments, novel approaches to prevention and treatment, as well as our strong collaborations with other NIH institutes and with the Substance Abuse and Mental Health Services Administration (SAMHSA).

INTRODUCTION

Drug abuse and addiction are a major burden to society; economic costs alone are estimated to exceed half a trillion dollars annually in the United States—including health, crime-related costs, and losses in productivity.¹ However, as staggering as these numbers are, they provide a limited perspective of the devastating consequences of this disease.

The National Institute on Drug Abuse, within the National Institutes of Health, is pleased to again report continuing declines in both licit and illicit drug use, particularly among our Nation's youth. In fact, NIDA's latest Monitoring the Future (MTF) survey results show a 23 percent decline over the last five years in any past-month illicit drug use by students in the 8th, 10th, and 12th grades combined. Declines in teen cigarette smoking, now at its lowest rate since the survey began in 1975, signal particularly good news since this will translate not only into decreases in cancer-related mortality but also decreases in deaths associated with the myriad medical consequences of smoking (i.e., chronic obstructive pulmonary disease, asthma, premature birth, sudden infant death syndrome, and more).

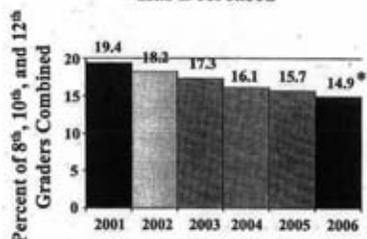
¹ Office of National Drug Policy (2004). *The Economic Costs of Drug Abuse in the United States: 1992–2002*. Washington, DC: Executive Office of the President (Publication No. 207303). 2004. Centers for Disease Control and Prevention. *Annual Smoking—Attributable Mortality, Years of Potential Life Lost, and Productivity Losses—United States, 1997–2001* Morbidity and Mortality Weekly Report 54(25):625–628, July 1, 2005. Harwood, H. *Updating Estimates of the Economic Costs of Alcohol Abuse in the United States: Estimates, Update Methods, and Data Report* prepared by the Lewin Group for the National Institute on Alcohol Abuse and Alcoholism, 2000. 2000.

Monitoring the Future Survey of Youth

Good News

23% Decline 2001 to 2006*

Past Month Use of Any Illicit Drug Has Decreased

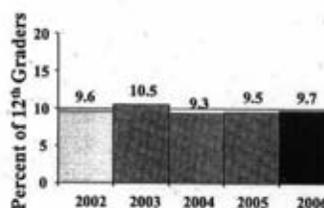


* $p < .001$

Troubling News

Nearly 1 in 10 Seniors Have Abused Vicodin

Past Year Nonmedical Use of Vicodin Remains High



Although abuse of most licit or illicit substances has decreased, such is not the case for prescription medications, particularly for opiate analgesics, which have produced steep increases in abuse-related emergency room admissions. The abuse of prescription medications occurs at all ages. However, it is particularly problematic in adolescents since this is the time when individuals are most vulnerable to addiction. The MTF revealed that in 2006, prescription medications, along with over-the-counter drugs (cough medicine), accounted for five of the top six drug abuse categories reported by 12th graders, marijuana still the most frequently abused illegal drug. Second in frequency of abuse was the prescription painkiller Vicodin, with roughly 1 in 10 seniors reporting abuse during the past year. Amphetamines ranked next, followed by over-the-counter cough medicines, with roughly 8 and 7 percent of 12th graders, respectively, reporting past-year abuse in 2006.

PREVENTION EFFORTS—GENES, ENVIRONMENT, AND DEVELOPMENT

Because adolescence is typically when drug abuse and addiction take hold, NIDA continues to focus research on this vulnerable period of development. Given that the brains of adolescents have not fully developed, including the connections between brain areas involved with emotions and areas involved with judgment and decision-making, adolescents are less able to exert inhibitory control over emotions and desires and are hence more likely to engage in risky behaviors, including drug experimentation. However, the brain at this stage is also inherently more plastic, which offers opportunities for prevention interventions that could lead to greater resilience.

Addiction results from the complex interaction of drugs, genes, and environmental and developmental factors. Thus NIDA has made the study of these interactions a priority, joining with other Institutes and organizations to support relevant research. Particularly relevant to substance abuse is the social environment, as genetic and imaging studies continue to reveal how the interplay of biological (i.e., genes, developmental stage) and social influences (i.e., family, peers, culture) affect individual choices and decisions about drugs. This knowledge is crucial to our future ability to tailor prevention interventions to address the risk areas of a given individual.

NIDA also encourages and supports the development of next generation technologies to identify and catalogue the multiple functional changes to the DNA (i.e., “epigenetic” modifications) that can result from environmental variables, such as quality of parenting, stress, and exposure to drugs. This avenue of approach requires support of research to develop standardized and comprehensive “phenotypes” of social environments (including family, peers, school, neighborhood, community, and culture) that can be monitored at various stages of a person’s life. A better understanding of the neurobiology of social behaviors is relevant both for the treat-

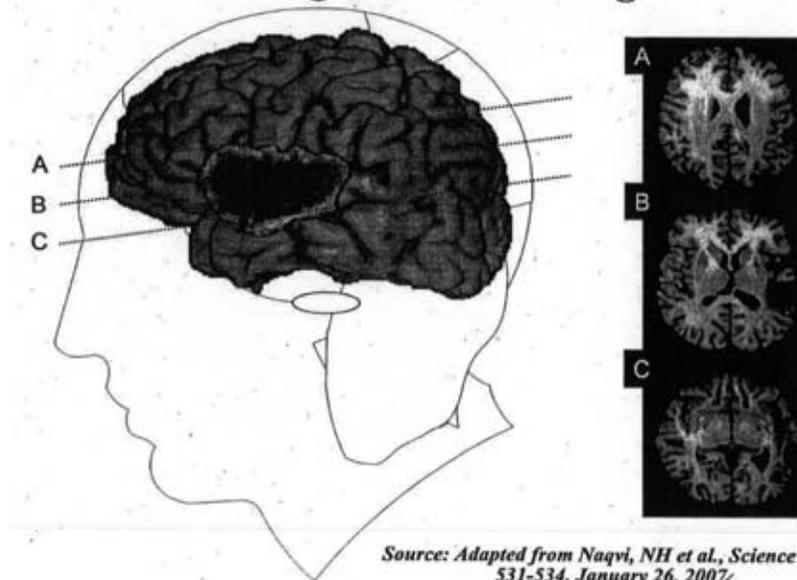
ment of drug addiction as well as mental illness, which also involves social aspects of human behavior and frequently co-occurs with substance abuse.

TREATMENTS—NOVEL APPROACHES

Historically, addiction therapies have targeted the brain's reward system to try and interfere with the pleasurable effects of drugs of abuse. Now, however, scientists have also identified the broader brain circuits that underlie fundamental aspects of drug abuse and addiction, such as craving, euphoria, motivation, learning, memory, interoception (i.e., sensitivity to internal stimuli such as hunger, pain), and inhibitory control—key contributors to addiction. These discoveries open wide the range of novel targets for different treatment approaches.

The recent discovery that stroke victims who suffered damage to their right insula (a brain area involved in emotional experience and interoception) dramatically reduced their smoking behavior points to new directions in addiction treatment. Specifically, findings suggest that strategies to noninvasively affect activity in the insula may be beneficial for addiction. These include use of technologies such as rTMS (repetitive transcranial magnetic stimulation), a noninvasive method to influence brain activity in specific regions, or “neurofeedback,” where patients learn to regulate specific regions in their brains by getting feedback from real-time brain images. Though not yet demonstrated for addiction, these techniques have shown promising results in depression and in the management of pain. They also open up a completely new way to develop psychotherapeutic interventions to target specific brain regions or circuits.

Damage to the Insula Disrupts Addiction to Cigarette Smoking



New knowledge of how proteins interact with one another in circuits implicated in addiction has prompted the development of novel addiction medications. For example, the cannabinoid receptor system, which regulates the activity of the dopamine system—the common target for the reinforcing effects of all drugs of abuse—holds promise for treating various drug addictions and, interestingly, for obesity as well.

Immunotherapeutic strategies offer another unique approach to relapse prevention. Such strategies are based on the development of vaccines to generate antibodies to the drug that block its entry into the brain and thereby interfere with its effects. Cocaine and nicotine vaccines are already in clinical trials, and NIDA has requested proposals to develop a methamphetamine vaccine.

PUTTING RESEARCH INTO PRACTICE

A major NIDA objective is to translate findings from basic and clinical research to guide and inform the design of prevention and treatment interventions that can be successfully implemented in real-world settings. People involved with the criminal justice system (6.9 million adult Americans) represent one such group. Approximately half of prison inmates meet criteria for alcohol/drug abuse or dependence, and yet the vast majority return to the community with no treatment.² In addition to the resulting high rate of recidivism for drug abuse and re-arrest, a recent study of inmates reported that untreated offenders were 12.7 times more likely to die within 2 weeks post-release than other state residents and that drug overdose accounted for 70 percent of those deaths.³ Because research has shown that treatment in the criminal justice system works, one of NIDA's initiatives is to support services research to help develop interventions that will be acceptable and sustained in the criminal justice system.

To this end, NIDA created and supports the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) initiative, an inter-agency collaboration aimed at bringing new treatment models into the criminal justice system to improve outcomes for drug-abusing offenders. To facilitate the translation of treatments to the criminal justice setting NIDA released a landmark publication entitled Principles of Drug Abuse Treatment for Criminal Justice Populations, designed to advance the concept of addiction as a brain disease and to summarize evidence-based principles for treating addiction in criminal justice settings.

NIDA's Drug Abuse Treatment Clinical Trials Network (CTN) also plays a key role in bringing evidence-based treatments to community settings by testing the effectiveness of new interventions and by training providers in the implementation of research based practices in order to promote their acceptance and adoption in the community. To further enhance the dissemination and utilization of research findings and to expand the involvement of the medical community in the screening and treatment of drug abuse, NIDA has launched a new "NIDA Goes to the Doctor" initiative. As part of this initiative, NIDA recently established four Centers of Excellence for Drug Abuse Information, in collaboration with the American Medical Association, with the aim of advancing addiction awareness, prevention, and treatment in primary care practices.

HIV/AIDS

Drug abuse plays a significant role in the spread of HIV, not only via injection drug use but also by increasing risky sexual behaviors. The addictive and intoxicating effects of many drugs can alter judgment and inhibition and lead people to engage in impulsive and unsafe behaviors. Drug abuse and addiction can also worsen the progression of HIV and its consequences, especially in the brain. Thus NIDA is supporting preclinical and clinical studies that examine the interactions between: drugs of abuse and HIV medication, HIV and plasticity (relative to changes that lead to addiction), and HIV and neurotoxicity (with regard to the adverse drug effects that result in neurodegenerative conditions such as dementia and parkinsonian symptoms).

While all groups are affected by HIV/AIDS, not all are affected equally. African Americans bear a disproportionate burden of HIV/AIDS in the United States, which may in part reflect data showing that African Americans are predominant among those who become aware of their infection at later stages in the disease process, and who therefore represent lost opportunities for treatment. Because early HIV detection helps prevent its transmission and increase health and longevity—and is as cost-effective as screening for other conditions such as breast cancer and high blood pressure—NIDA is supporting research to make testing more acceptable in communities nationwide. To this end, NIDA recently held a meeting aimed at improving the rates of HIV screening, and is now incorporating the resulting recommendations, which include addressing associated stigma and optimizing early diagnosis and follow-up linkages to care.

CONCLUSION

NIDA's comprehensive research portfolio is strategically positioned to capitalize on new scientific opportunities. Groundbreaking developments in the field of

²Mumola CJ and Karberg JC (2006) Drug use and dependence, state and federal prisoners, 2004 (NCJ 213530). Washington, D.C.:Bureau of Justice Statistics, U.S. Department of Justice.

³Binswanger IA, Stern MF, Deyo RA, Heagerty PJ, Cheadle A, Elmore JG, Koepsell TD (2007) Release from prison—A high risk of death for former inmates. *New Engl J Med* 356:157–65.

genomics signify an exciting era of research whereby we will be able to identify genes that make a person more vulnerable to drug abuse and addiction and devise counter strategies. We work toward a future in which early recognition of risk for addiction is no different than early recognition of other chronic medical diseases. Innovative use of imaging techniques allow scientists to design better treatments and more precisely judge their effectiveness, even predicting who would be most likely to benefit from selected therapies and who might be expected to relapse, so that preemptive interventions can be applied. Finally, advances in proteomics will help in designing much more sensitive tools to detect drug exposures and their consequences for individuals, heralding a future where diagnostic kits may be used to screen for drug abuse in the medical setting.

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

DRUG ABUSE FACTORS

Senator HARKIN. You were talking about adolescents who are exposed to a parent who is on drugs. What were the other factors that can increase the likelihood of addiction?

Dr. VOLKOW. A parent that is not there because he or she is incarcerated, physically abused, sexually abused, neglected, mental health problems in the family, low socioeconomic status, or poor access to education. These social stressors are increasing the risk of substance abuse.

Senator HARKIN. So a factor of 10 is pretty important.

Dr. VOLKOW. It is, dramatically.

Senator HARKIN. That is dramatic. So again it seems that drug abuse leads a lot of times I think to mental illness—am I correct in assuming that?

Dr. VOLKOW. Certainly there is unequivocal evidence that early exposure, for example, to nicotine can trigger anxiety disorders, even with those that do not have the genetic predisposition. There is also evidence that it increases the risk of depression. There is an enormous amount of discussion about the involvement of marijuana smoke on triggering psychosis or schizophrenia.

The thing is that it is happening, but probably depends upon having genetic vulnerability. What we do not know is can it trigger a schizophrenia-like disorder in someone that does not have the genetics.

So your answer is yes.

ADDICTION IN OTHER COUNTRIES

Senator HARKIN. Well, it seems to me that we ought to be paying more attention to this other area also.

Have you looked at addiction in the United States versus other countries?

Dr. VOLKOW. Yes, I have looked at this and the data are disturbing. The United States is at or near the top of most international prevalence comparisons across several types of illegal drugs.

Now, with respect to—

Senator HARKIN. That is illicit drug abuse?

Dr. VOLKOW. Illicit drug abuse. For nicotine, for example, the United States does much better than other countries in Europe and in Latin America. With alcohol there is tremendous variability. There the United States is not so high-ranking. There are certain

countries where the rate of abuse of alcohol is higher. It is in illicit substances that we are very, very high.

DRUG ABUSE BEING A CHRONIC DISEASE

Senator HARKIN. The only other point, just a very basic question. You talked about drug abuse being a chronic disease. How do we know it is really a disease?

Dr. VOLKOW. Well, there have been studies both in laboratory animals and in humans. In laboratory animals, for example, if you do repeated administration of drugs you can lead to compulsive administration of drugs in those animals. In animals you can actually sacrifice them and look at the biochemical changes linked with drug use and they have been shown to persist months after the animal has been discontinued from the drug intervention.

In humans now, with imaging technologies we can characterize the changes, both functional and biochemical, in the brain of people that are addicted. We followed—I used to do that before I became Director—these changes after the patients go through rehabilitation, and unfortunately many of them persist actually years after the person has stopped taking the drugs.

This is consonant with the phenomenology where we see individuals that have been able to stop taking drugs for years after rehabilitation, where something happens, usually a stressor—social stressors are one of the most powerful—and they relapse, even though they had not touched a drug in years, accentuating the notion that changes are still there, and so you become vulnerable. As long as you can manage the situation in your environment, you are okay, but if there is the stressor that puts you at very high risk.

Senator HARKIN. Senator Specter.

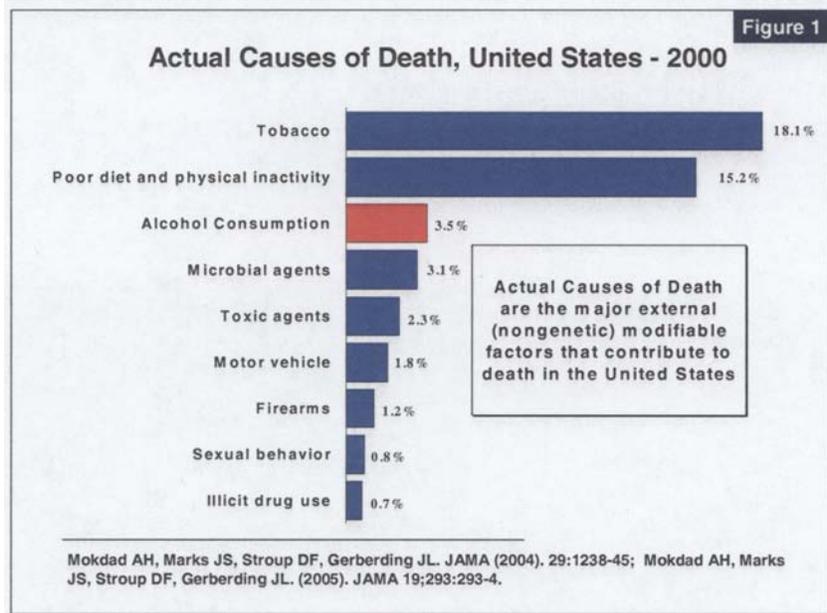
Senator SPECTER. No questions at this time.

Senator HARKIN. Now we move to Dr. T.K. Li. Appointed Director of the National Institute on Alcohol Abuse and Alcoholism in November 2002, Dr. Li got his undergraduate degree from Northwestern University, his M.D. from Harvard. Dr. Li, welcome. Please take about 5 minutes.

STATEMENT OF TING-KAI LI, M.D., DIRECTOR, NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

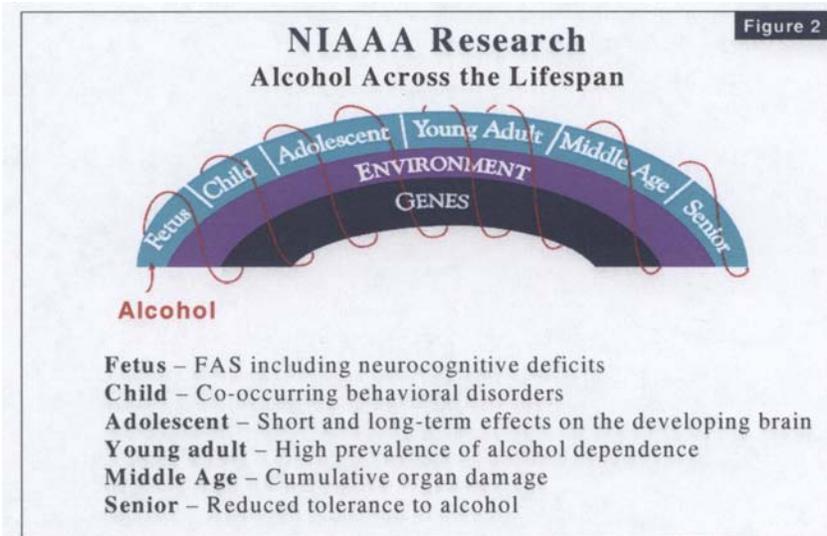
Dr. LI. Thank you, Senator Harkin, Senator Specter. I am pleased to be here with my colleagues to tell you about what NIAAA does and to update you on some of the new findings.

Let me first quantify the burden of illness attributed to alcohol. I think you have heard about the burden of illness due to mental health disorders and drug abuse. In terms of alcohol, let me just tell you that the HHS Centers for Disease Control and Prevention rank alcohol as the third highest actual cause of death, meaning that it is the third most preventable cause of death over this country, the first being tobacco and the second being poor diet and inactivity. See figure 1.



Alcoholism also is worldwide and is ranked as the third leading cause of disease in developed countries. It is a common disease. In this country, actually 1 out of 4 children are exposed in a family that has either alcohol abuse or alcohol dependence. Eighteen million people over the age of 18 have alcoholism and alcohol abuse. The cost estimated is \$185 billion.

Now, what I will show is a recent realization. See figure 2.



That is the variety and the kinds of alcohol problems people have is actually different depending on the stage of life. So we have crafted our research mission for alcohol across the lifespan, from fetus all the way to seniors. Again, as indicated, when ill health or diseases appear early in life, the burden of illness is high because of the long duration of the illness. That is a very important factor.

Therefore our mission is really to prevent and reduce harm as early in life as possible. This is preventing abnormal or high level patterns of drinking in pregnant mothers to those harmful patterns of use in children and adolescents, and then being able to predict the vulnerability factors as both you and Dr. Volkow have talked about and then target intervention for those who are at high risk for alcohol use disorders. Finally, we also want to personalize treatment in the afflicted individuals.

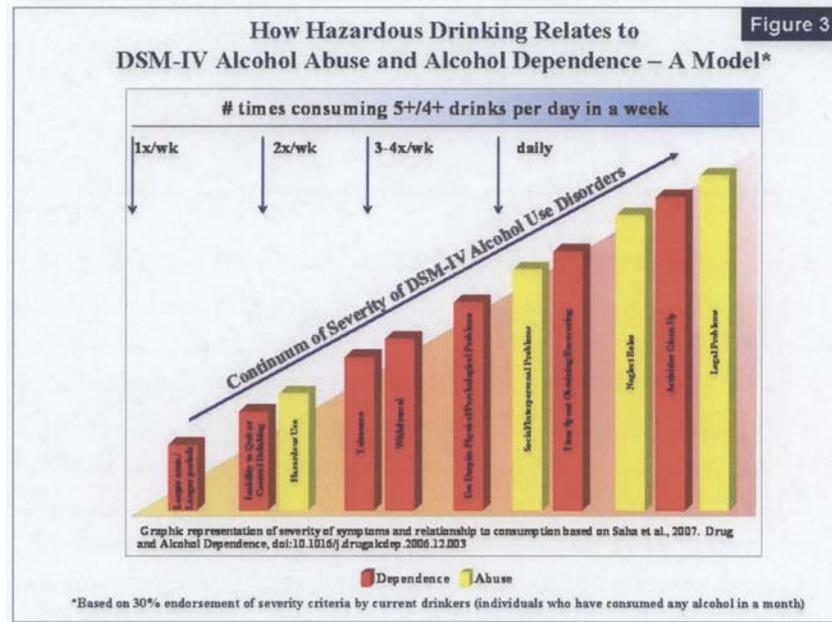
I will give you three examples of what it has been and what it is now and what we have for the future. First is that we have always thought—that is what I was taught and I think all of us at the table probably were—that alcoholism is a disease of mid-life, in other words people in their 40s and in their 50s. We now know that is not so. The highest prevalence of alcoholism is actually in our young people from age 18 to 24.

So in order to be able to be effective in treating and preventing the problem, we really should be looking to even the younger population. Therefore we are concentrating on and have a major initiative to study under-age drinking problems and how to prevent the problem. We are pleased to announce that on March 6 the Surgeon General issued a call to action to prevent and to reduce under-age drinking problems and our Institute was responsible for providing the science base for that report and we are going to be working with the Surgeon General in disseminating the actions that are proposed in that call to action.

Now, what is in the future? In the future, we are working actually with NIDA and with NIMH to look at what are the personality and temperament characteristics that predispose to harmful patterns of behavior in adolescence. I think this is an important common thread that speaks to comorbidity in this regard.

The other thing, the second thing we are trying to do, is to improve our way of diagnosing the problem. Again, the criteria we use to diagnose alcohol, drug and mental health disorders is really 1990s vintage. For example, for alcoholism it is called a maladaptive pattern of drinking that leads to significant impairment and stress, but it does not say what pattern or how much, nor can the diagnostic criteria be scaled.

Our research shows convincingly that we can scale it, the way of scaling both alcohol use and alcohol abuse and alcohol dependence by current diagnostics criteria and, as you can see in the figure here there is a single continuum of severity. See figure 3.



Shown here in red and yellow are the different criteria for abuse and dependence, scaled by severity.

The important question then is what pattern of drinking will predict this kind of severity of alcohol dependence? From our database we can say that if one drinks in a certain pattern, like drinking five or four drinks on an occasion, and you repeat this, then you can tap into the severity of alcohol use disorder scale, and this may be an important way of identifying those who are susceptible from their pattern of drinking.

How does this compare to the rest of medicine? Well, it is similar to being able to measure blood pressure and to measure cholesterol as a risk for having a future heart attack. Therefore, knowing what the blood pressure and cholesterol is, then you can treat that and you can interdict in terms of future problems.

So these are some of our current state of knowledge. We hope that we can be able to verify this pattern in the future and to use this in a clinical setting.

PREPARED STATEMENT

Finally, just to talk a bit about personalized medicine. Because of the advances in knowledge of molecular medicine, we are developing better and better medications to treat alcohol dependence once it has developed. These are our goals for the future. Thank you very much.

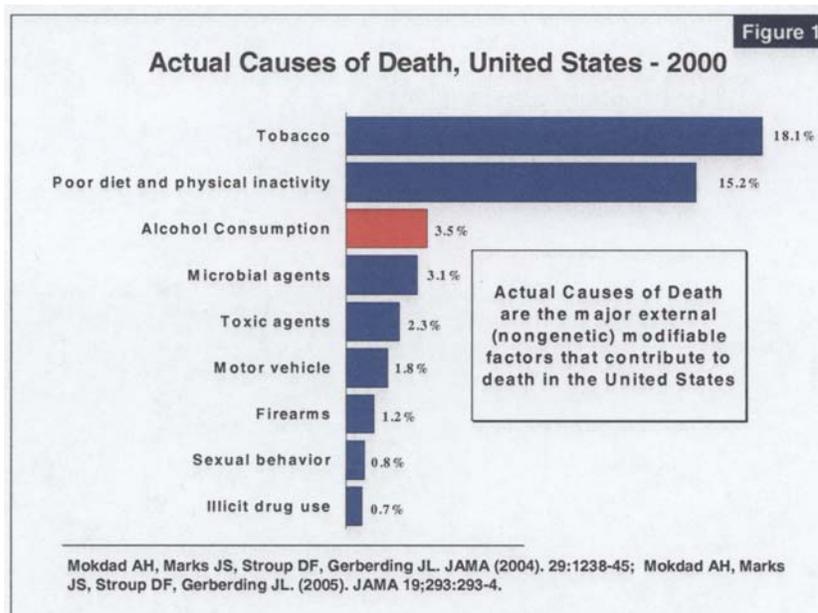
[The statement follows:]

PREPARED STATEMENT OF DR. TING-KAI LI

Mr. Chairman and Members of the Committee, thank you for giving me the opportunity to update you on the activities of the National Institute on Alcohol Abuse and

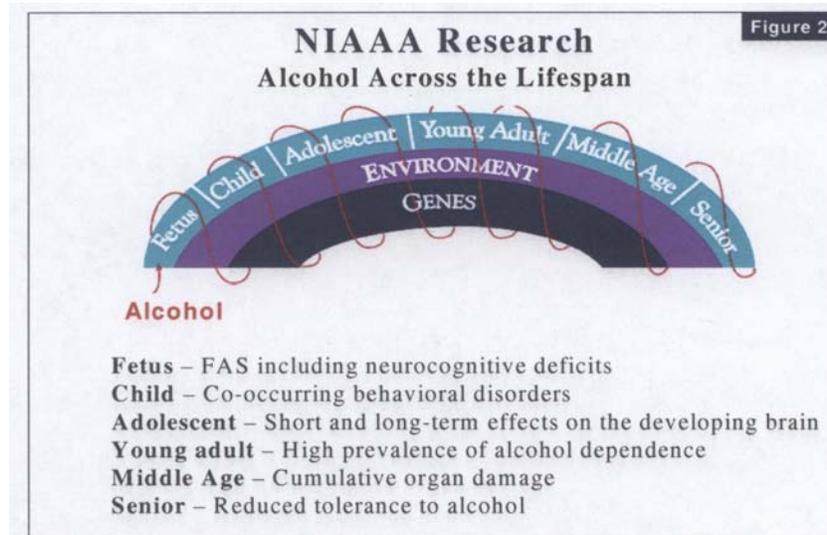
Alcoholism. I am Ting-Kai Li, Director of NIAAA, the lead agency for research on the health effects of alcohol. I am pleased to be here today with my distinguished colleagues from NINDS, NIMH, NIDA, and NIDCD to speak to the theme of Mind, Brain and Behavior. Those of us addressing you today have a fundamental mission—to reduce the substantial burden of illness caused by neurological and mental disorders, and by drug and alcohol abuse. Many of these disorders tend to manifest early in life, produce lifelong disability, derail individual potentials, and create tremendous burdens for families and significant cost to society. In fact, excessive alcohol use alone costs the United States an estimated \$185 billion annually.¹ The fiscal year 2008 budget for NIAAA includes \$436,505,000.

The HHS Centers for Disease Control and Prevention ranks alcohol as the third leading cause of preventable death in the United States (figure 1), and the World Health Report ranks alcohol as the third leading risk factor for disease in developed countries. Although alcohol primarily targets two organs, the brain and liver, it has a wide range of effects throughout the body and NIAAA's research portfolio encompasses all aspects of alcohol and health. In keeping with the theme of this Hearing, I will focus on the brain and behavior.



As illustrated in figure 2, alcohol can negatively affect the body and brain at all stages of life resulting in a range of consequences, including consequences from maternal alcohol consumption on the developing embryo/fetus to alcoholic liver disease and dementia in later life. Throughout the lifespan, it is important to recognize the contribution of developmental stage, individual differences—both genetic and environmental, and dose and duration of alcohol exposure to potential outcomes. The substantially different effects and consequences of alcohol exposure at different stages of life necessitate different research strategies.

¹Harwood, H. Updating Estimates of the Economic Costs of Alcohol Abuse in the United States: Estimates, Update Methods and Data (2000). <http://pubs.niaaa.nih.gov/publications/economic-2000/>



Today I would like to give you an overview of NIAAA's progress in three areas to reduce the burden of illness due to alcohol. First, I will describe prevention efforts focused on early life stages. Second, I will describe new findings that can be used to improve the diagnosis and early detection of alcohol use disorders (AUDs). Finally, I will describe efforts to personalize medicine for those suffering from alcohol dependence.

PREVENTION

Prevention is a key focus of NIAAA, especially for pregnant women, children and adolescents. By altering harmful drinking behavior we can significantly reduce the burden of illness due to alcohol. Exposure of the developing embryo/fetus can result in alcohol-induced birth defects, the most severe of which is fetal alcohol syndrome (FAS), a devastating developmental disorder that may include mental retardation. Individuals who do not exhibit the extent of symptoms characteristic of FAS may still have lifelong physical and/or neurological deficits as a result of in utero alcohol exposure. In addition, prenatal alcohol exposure itself may be a risk factor for subsequent alcohol dependence later in life. Therefore, NIAAA is supporting research to develop effective outreach to pregnant women, and approaches to intervene to protect against injury in the affected fetus and ameliorate deficits in the affected child.

Prevention in young children is also important, especially for those at high risk for early alcohol use. The period from birth to age 10 is a remarkable period of development, and although relatively few children in this age group are drinking alcohol, much is happening that will influence their path toward or away from early alcohol use. A number of the factors that put children at risk for early alcohol use are common to a wide range of adverse behavioral outcomes such as delinquency and other substance use. Even as young as preschool age, such children often have difficulties with impulse control and exhibit unusually high levels of aggression. NIAAA, NIMH, and NIDA are working to understand the personality/temperament characteristics that predispose to early-onset mental and alcohol/drug use disorders.

It is also essential to prevent and reduce underage alcohol use. Analyses of NIAAA's National Epidemiologic Survey on Alcohol-Related Conditions (NESARC) showed that 40 percent of individuals who reported drinking before the age of 15 also described their drinking behavior in a way consistent with a diagnosis of alcohol dependence. In fact, the highest prevalence of alcohol dependence in the United States occurs in the 18–24 year old age group. In addition, binge-drinking (i.e. drinking five or more drinks per occasion), which is popular with today's young people, results in acute consequences such as traffic fatalities, alcohol poisoning, suicides, homicides and drownings. Non-fatal, but potentially life altering consequences such as sexual assault and violence also result. As part of a larger effort focused on underage drinking research, NIAAA provided the scientific foundation for the

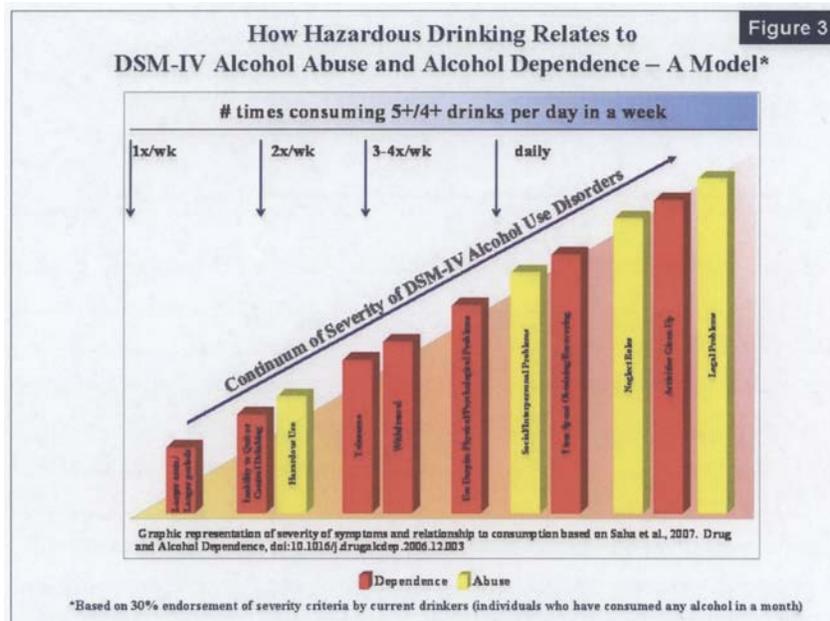
Surgeon General's Call to Action to Prevent and Reduce Underage Drinking and continues to inform the work of the Interagency Coordinating Committee on the Prevention of Underage Drinking.

Recognizing that the brain continues to develop throughout adolescence and into early adulthood, NIAAA is investing in research to determine the short and long-term effects of alcohol on the developing brain and the degree to which it can recover from these insults. Such studies, including one in collaboration with NIMH intramural scientists, may identify changes in brain wiring that are associated with dependence or affect cognitive functioning. In addition, given the difference in patterns of alcohol use between boys and girls as they move through adolescence, NIAAA is investigating the interplay of hormones, brain development and alcohol use.

DIAGNOSIS

It is important to identify individuals who are at risk for adverse alcohol-related health outcomes because of their drinking behavior. Excessive alcohol intake over time leads to cumulative organ damage, especially alcoholic liver disease and increased risk of coronary artery disease, stroke and dementia. Early diagnosis of harmful drinking would enable health care providers to intervene to prevent a range of adverse health outcomes.

As shown in figure 3, diagnostic criteria for Alcohol Abuse currently rely on an individual experiencing one or more alcohol-related problems associated with either the social or legal system, such as being cited for Driving While Intoxicated or problems with a spouse or family member. Diagnosis of Alcohol Dependence requires meeting three of seven criteria relating to physiological changes such as the development of tolerance to increased amounts of alcohol or the experience of withdrawal symptoms, behavioral maladaptation characterized by loss of control and compulsion to drink, and negative consequences from this drinking pattern. This categorical approach does not favor early diagnosis and intervention.



Today I report recent findings from analyses of NESARC that will improve the diagnosis of alcohol dependence. Further, alcohol abuse and dependence have long been treated as independent disorders. New findings indicate that they represent a continuum of severity of alcohol use problems. The analyses suggest we may be able to use questions that reveal an individual's pattern of drinking to identify the risk of developing AUDs. In much the same way that numerical measurements of blood pressure, cholesterol and triglycerides relate to relative risk for cardiovascular

disease, the best indicators of developing alcohol problems are measures of how frequently an individual engages in a harmful pattern of drinking. Specifically, recent findings relate data on the frequency of binge drinking and the maximum number of drinks consumed to risk for organ damage and to alcohol dependence. Through clinical studies, we may be able to determine appropriate cut points to define AUDs and also to gauge one's risk of developing alcohol problems. Just as physicians treat high cholesterol before an individual experiences a heart attack, they will be able to intervene before an individual loses control of drinking. Diagnosis centered on harmful drinking patterns should also help health care providers differentiate between alcohol related neurocognitive deficits in the elderly and Alzheimer related dementia.

MEDICATIONS DEVELOPMENT

NIAAA is supporting research on a number of fronts to improve treatment options for alcohol dependence. Studies in animal models focusing on signaling pathways in the brain have produced additional targets for human studies. For example, the anxiety that people with alcohol dependence experience when they stop drinking is a powerful motivator for them to resume. In addition, stress can trigger relapse to heavy drinking after a period of abstinence. Therefore, medications are being tested that target molecules involved in biological pathways that mediate stress and anxiety such as corticotrophin-releasing factor, neuropeptide Y, and nociceptin receptors. Also being tested are medications that target the metabolism of endocannabinoids, naturally occurring substances in the brain that act on the same receptors as the active ingredients of marijuana and have been shown to play a role in regulating appetite for alcohol.

TREATMENT RESEARCH

In addition to developing new medications and determining the genetic and environmental factors that contribute to the initiation and escalation of drinking, it is equally important to understand how individuals change harmful drinking patterns. The majority of young adults change harmful drinking behaviors without treatment. Adults seek treatment when alcohol dependence becomes chronic and relapsing, generally in the period of midlife. Data from clinical trials raise the question of whether treatment itself is responsible for the improvement in drinking behavior or if the positive motivation to seek treatment actually underlies a substantial part of the treatment success. Further, evidence has shown that a wide array of available therapeutic approaches yields similar results, suggesting that it is not the particular technique that is responsible for change but other common underlying factors. As a result, NIAAA is focusing on addressing underlying mechanisms of change across all behavioral treatments, identifying the factors that contribute to behavioral change and lead to sustained recovery. This research will improve clinical practice both by identifying key aspects of therapy that must be present for maximum effectiveness and by facilitating the delivery of more finely tuned individualized treatment. We also need to be particularly mindful of health disparities. A recent study suggests that Hispanics and Blacks with higher levels of problem severity were less likely to have used treatment services than Whites with problems of comparable severity.

Taken together, these strategies of improved prevention, better diagnosis and personalized treatment are expected to reduce the burden of alcohol-related illnesses over the long term and lead to better health outcomes for the nearly 18 million American adults who, in any year, struggle with alcohol use disorders.²

MEDICATIONS FOR ALCOHOL DEPENDENCE

Senator HARKIN. Well, now that you are on that, what medications?

Dr. LI. Well, we have several. Fifteen years ago all we had was Antabuse. Now in the last 8 years or so we have approved two other medications. One is Naltrex, both orally taken and also by injection; and third is a medication called Acamprosate. So these drugs seem to work better for certain aspects of alcohol dependence based on severity. We have others in the pipeline being developed

² Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, and Pickering RP. Drug and Alcohol Dependence 2004. 74: 223–234.

that will target different molecules, different receptors, and these are an important vision for the future.

NIAAA OUTREACH

Senator HARKIN. Doctor, every Institute out there needs to do outreach. Every Institute does outreach to the communities around the country.

Dr. Li. Yes, sir.

Senator HARKIN. How well are you doing in reaching out to States and local communities to put into practice some of your findings?

Dr. Li. The three so-called ADM Institutes, we are fortunate in that we have a partner in this regard. That is SAMHSA. This was created before the three Institutes joined NIH. So we do have a partner out there that does the outreach. We work with them as well as ourselves in promoting, providing the outreach to the public. I think that we do this together. There is an inter-agency group that does this.

Senator HARKIN. So you are doing outreach?

Dr. Li. Yes, sir.

ALCOHOL ADVERTISING

Senator HARKIN. Well, I would like to know more about how that is done. I will get my staff to get some more information on it.

I wonder about messages that young people receive about drinking, all the advertising about the glamorizing of drinking alcohol. Of course, it is a free country. People can advertise. But I just wonder about the impact of these messages and how they are reinforcing young people that it is all right to drink and it is all right to maybe even drink a lot, although I noticed that some of the beverage companies, if they want to be called that, are now putting out things about being responsible in drinking. I see a lot of that advertising going on.

But I am just wondering about the messages young people get about drinking. What have you looked into that? How have you looked into that?

Dr. Li. I think this is a very complex issue because there are a lot of background of messages coming in, and the advertising is only one part of it. So how children respond to advertising is a little different depending on how old they are and what their context.

Senator HARKIN. Are you doing any research into this?

Dr. Li. Yes, sir.

Senator HARKIN. You are doing some research in that, the different messages and how young people are affected by this?

Dr. Li. Yes.

Senator HARKIN. Any results?

Dr. Li. Well, we have some, but as I said, it is difficult to be able to dissect out which part is advertising that causes an increase in drinking or whether all they are doing is changing brands. I think the issue is whether there is an increase in drinking because of advertising but data on that is very, very slim. I mean, the result is that it is not a major influence.

BINGE DRINKING

Senator HARKIN. What kind of research are you doing into binge drinking, especially among college students?

Dr. LI. Binge drinking on that model there is the most harmful pattern, because physiologically it makes sense. You need that much drinking in order to get your blood alcohol to a level that is impairing and that is the nature of binge drinking, namely drinking to intoxication. Why people do it is something we would love to find out.

Senator HARKIN. Are you doing research into this?

Dr. LI. Yes, we are. It has to do with expectancies, it relates to problems which are stress and stressors. When we talk to people, young people, why are you drinking, they say, I want to drink because I want to get drunk. So it is a different approach.

You must understand that alcohol is the most ancient intoxicant, mind-altering drug. There is a lot of history there, and to be able to change the culture and what people think of it is not easy.

Senator HARKIN. One of the biggest fears that parents have when their kids go off to college is just this, binge drinking. I do not know the answer to it, but I just wonder if we are doing any research into that, what is happening, how it is happening, what is motivating young people to do this. I do not know. I do not have the answer to that.

Dr. LI. We have, for example, a site demonstration project on college drinking. This is a cooperative agreement. It is a demonstration project to look into that, and the study is now in its fourth year. I have been on the job 4 years. This is something we started when I took over.

We also have eight or more sites to study under-age drinking, meaning in adolescents, in high school level and middle school level.

CRIMINAL JUSTICE SYSTEM

Senator SPECTER. A few questions now, Mr. Chairman.

Dr. Volkow, since I was district attorney in Philadelphia many years ago the incidence of drug addiction has been a causative factor in 70 percent of the crimes, and we have not been willing to invest in realistic rehabilitation to try to stop the chain of recidivism. Is there any answer from your research to deal with drug addiction which is within the financial reach of what society is prepared to spend on corrections?

Dr. VOLKOW. Absolutely. In part one of our priorities is the criminal justice system, because—

Senator SPECTER. You said absolutely not?

Dr. VOLKOW. No. Absolutely. It is extraordinarily important to actually target substance abuse treatment in the criminal justice system. Data have—

Senator SPECTER. How do we deal with it effectively within some reasonable cost parameter?

Dr. VOLKOW. You save out of every \$4—out of every \$1 that you spend on treatment in the criminal justice system, you save \$4.

Senator SPECTER. I am not interested in how much you save. I am interested in how much we spend. I am interested in how we

get my colleagues to spend money for corrections, and the inquiry goes to whether there is any answer within what the cheapskates in government are willing to spend, to ask the question more specifically.

Dr. VOLKOW. The cost, what I can tell you, the cost for a treatment program on substance abuse is around \$10,000 in the criminal justice system, and it is \$20,000 to incarcerate an individual, correct, more or less, on average? So that gets you an idea.

Senator SPECTER. There is a willingness to spend money for incarceration.

Dr. VOLKOW. Correct.

BRAIN INJURY AND ALCOHOL

Senator SPECTER. But not for rehabilitation.

Dr. Li, I have heard martini drinkers, illustratively, express concern about killing brain cells with the alcohol. Is that a real risk?

Senator HARKIN. Just martinis?

Senator SPECTER. That is what I drink.

Dr. Li. We know alcohol kills brain cells.

Senator SPECTER. It does kill brain cells?

Dr. Li. Yes, sir.

Senator SPECTER. How many and at what rate?

Dr. Li. I do not know the rate or the number. But we certainly—

Senator SPECTER. Is it a real danger?

Dr. Li. It is a result. Is it a real danger to whom?

Senator SPECTER. To the people who drink the martinis.

Dr. Li. Certainly over long periods of time, yes, sir.

Senator SPECTER. What would be consumption so that you do not become an alcoholic or to a lesser extent impair your brain?

Dr. Li. Well, this is exactly the kind of research we want to do, to be able to do to put a quantitative basis to the clinical observations—

Senator SPECTER. How much more money do you need than \$30 billion that Senator Harkin has provided for you?

Dr. Li. We have just over \$400 million for our Institute's appropriation.

Senator SPECTER. Dr. Landis, you are the chairman of the stem cell—

Senator HARKIN. Could we just finish their testimony so I can get their testimony before?

Senator SPECTER. That was my suggestion.

Senator HARKIN. I would like to turn to the other Institutes and have them at least make their presentations before we ask for questions.

TRAUMATIC BRAIN INJURY

Senator SPECTER. All right. I will go to Dr. Insel.

We talk a lot about the 3,200 or more men and women killed in Iraq. We now find that there are an enormous number coming back from Iraq with brain injuries. We do not focus as much on the 24,000-plus who have been injured in Iraq. Now medical procedures can save lives, but with very material brain impairment. There are reports that these young men and women are coming

back in their 20s, teens, and that they are going to need care for a lifetime.

To what extent can you evaluate those kinds of brain injuries and what might be done to provide therapy from the kind of research you are undertaking?

Dr. INSEL. I am going to leave the traumatic brain injury question to Dr. Landis, whose Institute is more involved with that. Let me add what you did not say, which was that the greatest proportion are coming back with what looks like post-traumatic stress disorder. The numbers are significant: 1.4 million individuals have served in Iraq and Afghanistan. The rate now already is about 12–13 percent PTSD. My calculation is about 170,000 people who will have PTSD currently or in the next couple of years.

We know that after the Vietnam War the rate went up to between 20 and 30 percent overall, so even higher than where we are now. So you are talking about a very significant amount of disability and high cost. Eighty percent of the time in the Vietnam case this was associated with substance abuse, usually drug addiction, often leading to criminal behavior as well—a tremendous disability at a very high rate from a mental disorder that is trauma-induced.

Senator SPECTER. Well, what should be the governmental response, either through the Veterans Administration of the Department of Defense, so that these young men and women and their families do not have to bear the burden and the cost when it is really not a war of their choosing and their making, but a war for the Government, that ought to be borne by the Government? What is an equitable response by the Government to these kinds of injuries?

Dr. INSEL. Let me talk about what the science can tell us, because I think that is where the biggest hope may be. I think we can use the science we have now to develop better treatments, and that is part of why we have got a major effort with the VA and DOD to do just that. More importantly, what we do not know is who is going to be sensitive to this. So if 100 people come back, 13 of them will develop PTSD currently. We would like to know who those 13 are and be able to preempt this, actually help them to recover before they develop the full syndrome. That is right now the target for the intervention.

Senator SPECTER. Thank you very much.

Thank you, Mr. Chairman. Let me comment that I think this procedure is a good one and the informality is conducive to a little easier reparte. I regret that I have to excuse myself. We are very heavily engaged right now with the U.S. Attorneys and I have to tend to that this afternoon. But Senator Taylor will be here in my place and I will be following it closely. I know that Senator Harkin joins me in this. We will provide the kinds of resources you need to the maximum extent of our capabilities, which is now more limited than it used to be. Thank you.

Senator HARKIN. That is true. That is very true. Well, thank you very much.

Now we will turn to Dr. James Battey, who has served as Director of the National Institute on Deafness and Other Communications Disorder since 1998. Dr. Battey got his B.S. from the Cali-

fornia Institute of Technology and his M.D. and Ph.D. degrees from Stanford.

Dr. Battey, please proceed.

STATEMENT OF JAMES F. BATTEY, JR., M.D., DIRECTOR, NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATIONS DISORDERS

Dr. BATTEY. Thank you very much, Mr. Specter and Mr. Harkin. It is a pleasure to be here today and I would like to begin by thanking you for your time, interest, and support over the years. It is deeply appreciated by those of us at NIH and in particular by the research community that we serve.

If I could direct your attention to figure 1. I am going to refer to some things on them.

Senator HARKIN. By the way, I want you to know I appreciate the fact that all of you gave me your testimony last week. I was able to look at it over the weekend. I appreciate that very much.

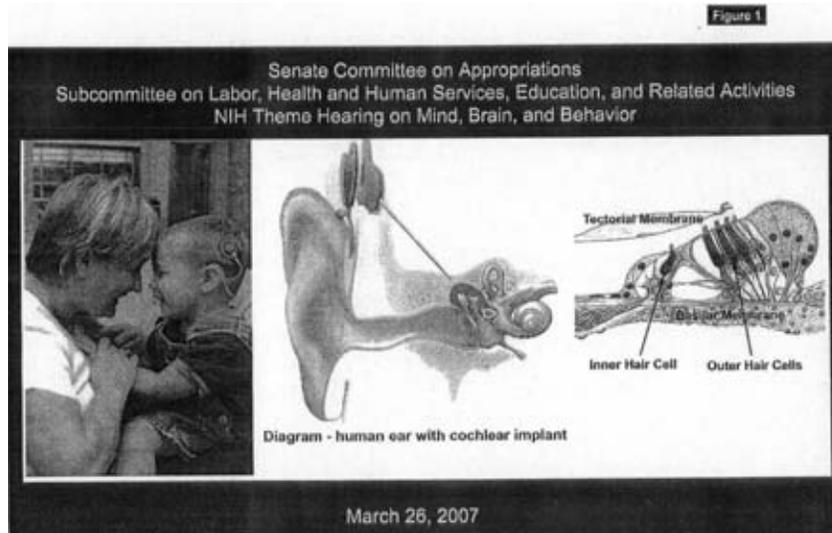
Dr. BATTEY. It is a particular pleasure to be here with my colleagues with whom I work every single day and to share the wonderful things that are happening in their Institutes and tell you a little bit about what is happening with NIDCD.

If you turned back the clock to the beginning of the 20th century, most Americans made their living with physical labor and did not really need great communications skills or a well-trained mind. But here as we enter the 21st century the situation is entirely different. The good jobs, the interesting jobs, the important jobs, the high-paying jobs, all involve an intact mind that is not impaired by drugs or alcohol, that is not bedeviled by mental illness, that allows one to communicate effectively.

One of the most important issues with communicating effectively is hearing impairment. It is one of the most common causes of a communication disorder and we estimate that roughly one American in six has a significant communication disorder that compromises their ability to access these high-paying, high quality jobs.

HOW HEARING HAPPENS

Now, to help you understand what we are trying to do about this problem, I would like to introduce you to the science behind how we hear. Now, if you can focus your attention for a moment on the center image, you will see a pink snail-shaped structure. See figure 1. That is the cochlea. A cross-section across that cochlea is shown in the right-hand image.



You will see four little blue cells with some little projections coming out of the top of them. Those four cells are called hair cells, and it is nanometer deflections of those little tufts that signal hearing and tell those cells to send an electrochemical impulse to the brain. That is how we hear.

These hair cells are the weak link. They are the vulnerable aspect of the hearing organ. They are what is generally lost or never developed in individuals who either cannot hear from birth or lose their hearing progressively throughout their life.

As long as there are some hair cells left we can amplify sound with a hearing aid and help those individuals hear. But when virtually all the hair cells are gone, amplification simply does not work. That is where research, supported initially by NINDS and then by NIDCD after we became an institute in 1988, on the cochlear implant has changed everything.

COCHLEAR IMPLANTS

There is a picture of a child on the left-hand side wearing a cochlear implant, which is also shown in an image in the center. It is an array of 22 electrodes that a surgeon inserts into that snail-shaped cochlea. See figure 1. It coils around and bypasses the damaged hair cells, stimulating the hearing nerve directly.

In an adult that loses their hearing, the cochlear implant can often restore the ability to understand speech to the point where that deaf individual can now use the telephone. In a young child who is born unable to hear, cochlear implantation before the second year of life can result in that child being mainstreamed in normal schools and be on grade level for language literacy and spoken skills. This is really an enormous testament to the plasticity of the human brain, to be able to go from losing 30,000 hair cells, replace it by stimulation from 22 electrodes, and still have the brain be

able to interpret what it hears as speech. I consider this to be simply remarkable.

HAIR CELL REGENERATION

But it would be far better to replace the hair cells that have been lost, to undo the damage, rather than simply bypass it with an array of electrodes. Birds and fish can regenerate their hair cells if they are damaged. Mammals and humans cannot. We are looking to understand why there is this difference between species who can regenerate hair cells and why others cannot. We are beginning to understand the molecular mechanisms that underlie how hair cells develop in the first place and also how potentially regenerated.

PREPARED STATEMENT

For example, recent studies supported by NIH have shown that there is a master regulatory gene called *Math-1* whose expression is necessary and sufficient for hair cells to develop in the first place. Animal models missing the *Math-1* gene never develop hair cells and are deaf. We have preliminary data from one laboratory that they can, by stimulating the expression of *Math-1* in an animal model that has been deafened by damaging the hair cells, that partial hair cell regeneration could take place and perception of sound can be restored, which gives us the hope that the day may come some day when, instead of simply bypassing damaged hair cells, we can regenerate new ones and provide a whole new approach to helping individuals who have lost their hearing.

Thanks very much for your attention and I will do the best I can to answer any questions you might have.

[The statement follows:]

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

Mr. Chairman and Members of the Subcommittee: I present the President's budget request for the National Institute on Deafness and Other Communication Disorders (NIDCD). The fiscal year 2008 budget for NIDCD includes \$393,682,000. The NIDCD conducts and supports research and research training in the normal and disordered processes of hearing, balance, smell, taste, voice, speech, and language. These processes are fundamental to the way we perceive the world and to our ability to communicate effectively in modern society. Disorders of communication impose significant economic, social, and personal costs. Accordingly, the goal of the NIDCD strategy is to produce outcomes with a significant impact on the health of Americans. Driven by the public health need and scientific opportunity identified in the NIDCD Strategic Plan, NIDCD prioritizes its research investment to fund the most promising scientific opportunities in diagnosis and treatment of communication disorders. The following are notable highlights from the past year that are the result of NIDCD support:

GENES AND COMMUNICATION DISORDERS

The NIDCD recognizes that functional genomics—determining the identity, structure, and function of genes—is one of the most rapidly developing areas of research. Inherited genes account for approximately 50–60 percent of the severe to profound cases of childhood hearing loss. NIDCD scientists are working to understand the normal function of these genes, and how they are altered in individuals with communication disorders (such as hearing loss, stuttering, speech-sound disorders, autism, and dyslexia). These research investments to understand the genetic basis of communication disorders will help scientists develop diagnostic tests and better treatments for the millions of Americans with hereditary hearing impairment.

PREVENTING AND DIAGNOSING COMMUNICATION DISORDERS

The Centers for Disease Control and Prevention (CDC) reports that two to three out of 1,000 babies born each year in the United States have a detectable hearing loss, and estimates the average lifetime cost for one individual with hearing loss to be \$417,000 (in 2003 dollars). Accordingly, NIDCD places a high priority on understanding causes, possible treatments, and progression of hearing loss during early childhood. NIDCD-supported research demonstrates that children not exposed to language during their first 3 years of life due to hearing loss will have more difficulty developing spoken or signed language and reading skills. Early identification of hearing loss enables parents to pursue interventions early enough that their child can learn to communicate on par with his or her hearing peers.

However, childhood hearing loss does not always show up right away. Congenital cytomegalovirus (CMV) is the most common viral infection passed from a mother to her unborn child, with 40,000 infants born infected each year. According to the CDC, approximately 10 to 15 percent of these children have some degree of hearing loss. Scientists believe that CMV infection present at birth is a leading cause of sensorineural hearing loss in children. Hospitals do not test newborns for CMV unless they already show signs of the disease. NIDCD is funding the CMV and Hearing Multicenter Screening (CHIMES) Study to identify asymptomatic children and follow them to determine if hearing loss develops. Scientists will screen approximately 100,000 children at birth for CMV infection, and those who test positive will undergo follow-up diagnostic hearing testing to determine the onset, severity, and progression of hearing loss. The scientists will use these data to understand the relationship between CMV infection and hearing loss and to determine whether CMV screening together with hearing testing can improve the detection and prediction of permanent hearing loss in children.

Although success in establishing early screening programs has identified a new population of children with hearing loss, we do not know which interventions provide the best outcomes. Current intervention and outcome data are limited to those children whose hearing loss was detected later in life. Hearing health specialists need research data that considers not only the intervention strategy but also the parent-child interaction, socio-economic factors, and language exposure. To address this need, NIDCD held a workshop on "Outcomes in the Child with Hearing Loss" in December 2006. NIDCD is using information from this workshop to develop fiscal year 2008 initiatives focused on prospective and longitudinal research. These initiatives will be part of a multi-agency collaboration designed to close the gap between children with hearing loss and their hearing peers, and will provide sorely-needed information on the best strategies to achieve this goal.

DEVELOPING ASSISTIVE DEVICES

NIDCD-supported basic research on the ears of the tiny fly *Ormia ochracea* has inspired a new generation of hearing aids. The fly's ear structure permits ultra-sensitive time coding and localization of sound, and scientists used it as a model to develop miniature directional hearing aid microphones that can selectively amplify speech rather than amplifying all sounds. NIDCD-supported scientists are now working to make these directional hearing aids widely available. Individuals with hearing loss who use hearing aids fitted with these improved directional microphones will experience improved quality of life because the aids will do a better job of helping them to understand spoken language amidst background noise.

Some individuals with severe to profound sensorineural hearing loss may benefit from a cochlear implant (CI). The NIH's support has played a significant and important role in the development of CI technology over the last three decades. A CI converts sound into electrical impulses on an array of electrodes surgically inserted into the inner ear, bypassing the damaged hair cells that normally detect sound. The CI stimulates the auditory nerve directly and restores the perception of sound to individuals who are deaf.

The Food and Drug Administration (FDA) estimates that approximately 36,000 Americans have received CIs, and one-half of the recipients were children. The FDA approved the use of CIs in children as young as 12 months of age. NIDCD-supported research demonstrates that the sooner a child with profound hearing impairment receives the benefit of a CI, the greater the benefits and improvements in speech perception and language production. Because of the rapid development and plasticity of their brains, young children implanted with a CI usually show age-appropriate brain responses within 6 to 9 months after the CI is turned on.

CIs are expensive (costing approximately \$60,000 for the device, associated surgical expenses, and postoperative fitting and training) and many insurance companies were initially unwilling to reimburse for this cost, citing a lack of evidence that

the device is cost-effective. To address this concern, NIDCD-supported scientists conducted an initial cost-utility analysis of the CI in children to examine whether the benefits of the implant outweigh its costs. The study showed that CIs improve the children's quality of life, and result in a net saving to society. The cost benefit is the result of fewer demands on special education and greater wage-earning opportunities for CI recipients, providing an estimated life savings per child at \$53,198. This landmark study has helped make CIs a standard treatment for severe-to-profound nerve deafness, and many insurance companies now cover them.

An NIDCD-supported study assessed the sound-localization abilities of children (ages 5 to 14 years) wearing two cochlear implants as compared to one. Children in the study located the source of a sound more accurately when they were wearing two implants as opposed to one. The greater the experience with two implants, the more adept he or she became at localizing sound. The research team is now investigating the effects of bilateral implants on word learning and language acquisition in infants and toddlers receiving CIs at a young age.

NIDCD-supported scientists are currently using lessons learned from their cochlear implant research experiences to develop an implanted device to help restore the sense of balance. The prototype vestibular implant has the potential to benefit over 90 million Americans who have experienced a dizziness or balance problem.

STRATEGIES TO PROTECT YOUR HEARING

The NIDCD shares Congress's concerns that approximately 10 percent (over 22 million) of American adults have suffered permanent damage to their hearing from exposure to loud sounds or noise at work or in leisure activities (CDC NHANES). In 1999, the NIDCD collaborated with the National Institute for Occupational Safety and Health (NIOSH) to launch WISE EARS!. WISE EARS! is a national campaign to prevent noise-induced hearing loss (NIHL) in the general public, including the workplace. NIDCD has built a coalition of nearly 90 partner organizations and disseminated information and promotional materials through the media, at professional conferences and health fairs, and over the Internet. In 2006, the NIDCD conducted an evaluation on the WISE EARS! Public Health Campaign to obtain an accurate picture of how far WISE EARS! has progressed in achieving its goals and to identify those needs that have not yet been addressed through current educational and promotional methods.

Finally, Mr. Chairman, I would like to thank you and members of this subcommittee for giving me the opportunity today to present exciting scientific advances from the NIDCD. I am pleased to answer any questions that you have.

REGENERATION OF HAIR CELLS

Senator HARKIN. Dr. Battey, thank you very much.

Let us get into the whole thing of regeneration of hair cells. I do not remember the exact year, but somewhere around 1990, 1991, I remember getting a paper on the regeneration of hair cells and how certain birds exhibited the fact that they could regenerate hair cells.

I engaged in questions with the then-Director—

Dr. BATTEY. Is that James Snow?

Senator HARKIN. Dr. Snow, thank you very much. Dr. Snow, about that. Yes, and I have asked that question repeatedly. That is at least 17 years ago and almost what I hear you saying is what I heard 17 years ago. Are you telling me—

Dr. BATTEY. Seventeen years ago we were not regenerating hair cells in mammals.

Senator HARKIN. Are you now?

Dr. BATTEY. Yes, we are. In a guinea pig model—

Senator HARKIN. I thought you told me that it was just birds.

Dr. BATTEY. They can do it spontaneously. In a guinea pig animal model that is deafened—I do not do it; Yehoash Raphael does it at the University of Michigan—that deafens the animal in one ear by administering a drug called gentomycin, he can then express *Math-1* in that inner ear and see hair cells regenerate, and can

show physiological evidence of auditory percept in the ear that had been deafened.

Senator HARKIN. How long has he been doing this?

Dr. BATTEY. I would have to go back to look. I think Yehoash's paper is from 2005.

Senator HARKIN. Recent.

Dr. BATTEY. Yes.

Senator HARKIN. Is there more than one locus of this research going on right now?

Dr. BATTEY. It is now being studied in other laboratories and others are hopefully going to replicate his findings. And then maybe if that works out we will move forward to non-human primates, with the hope of ultimately moving into phase 1 clinical trials.

Senator HARKIN. When do you think you will be ready to go to higher mammals?

Dr. BATTEY. I really do not know. I could give you a guess, but it would be nothing better than a guess.

Senator HARKIN. Well, you are funding this research?

Dr. BATTEY. Yes.

Senator HARKIN. Where is that? University of where?

Dr. BATTEY. University of Michigan.

Senator HARKIN. Michigan. Well, if they have been doing guinea pigs for a couple years and they have gotten some pretty good results, I am just wondering how soon they might be ready to take it to a higher order of mammals.

Dr. BATTEY. I would say if it replicates nicely in several other laboratories, which is the cornerstone of good science, then we would be ready to try to stimulate research in non-human primates. It is a couple of years.

Senator HARKIN. This is a genetic intervention?

Dr. BATTEY. Yehoash's work—I am going to get technical here a little bit—it is a viral vector that expresses a gene called *Math-1*, which is a master regulatory gene.

Senator HARKIN. Are you saying "MATH?"

Dr. BATTEY. MATH, M-A-T-H, dash 1.

Senator HARKIN. *Math-1*.

Dr. BATTEY. It stands for Mouse Atonal Homolog 1.

Senator HARKIN. That is a little bit hard for me, okay.

Dr. BATTEY. I warned you.

Senator HARKIN. It is a viral vector. I understand that. Yes, I do have a good feel for that. But I do not know that much about how much regeneration they have had and a percentage. Is it like 10 percent of the hair cells are restored, is it 20, 30? Do you have any idea?

Dr. BATTEY. Roughly a third.

Senator HARKIN. About a third?

Dr. BATTEY. Yes. Again, it varies from animal to animal exactly how well this works.

Senator HARKIN. I thought you said they were just doing it in guinea pigs.

Dr. BATTEY. I am sorry, from guinea pig to guinea pig.

Unfortunately, you have to do it in a number of guinea pigs to show if the result is reproducible.

Senator HARKIN. A big question then, why is it more in some and less than others.

Dr. BATTEY. It is a great question. Probably there are other genes involved as well. The genetic background may be different in one guinea pig than another.

Senator HARKIN. But that is kind of the holy grail of this, of what we are looking at in terms of deafness, right?

Dr. BATTEY. Hair cell regeneration would be wonderful, not just for hearing impairment, but also for balance disorders, because there are another class of hair cells in the balance organ, which is that part of the inner ear that is right next to the snail-shaped cochlea.

Senator HARKIN. Which is why so many older people fall and break hips and stuff. As you get older you lose your sense of balance.

Dr. BATTEY. Yes, roughly—well, dizziness is the most common reason why an elderly person consults a physician.

Senator HARKIN. Well, I would like to know more. Anything that you have got on what they are doing at Michigan in any kind of a form that I can halfway understand, I would appreciate seeing it.

Dr. BATTEY. I will have my staff abstract something in educated lay terms describing the results from the University of Michigan.

Senator HARKIN. I appreciate that. How many more universities are doing this? What is their timetable, that type of thing.

Dr. BATTEY. We will get that information for you.

Senator HARKIN. I would like to know about that. Understand my concern. I have been hearing about this. Seventeen years I have been hearing about regenerating hair cells.

Dr. BATTEY. It is a hard problem.

Senator HARKIN. Well, I understand.

Dr. BATTEY. I wish that science progressed faster, but usually our understanding is incremental and often it is serendipitous. For example, the discovery of the importance of the *Math-1* gene took place in a lab that was not interested in hearing at all. They simply knocked the gene out in a mouse and the mouse was deaf.

Senator HARKIN. Fascinating.

Well, that is all I have for right now. I may have others. Now we will turn to the National Institute of Neurological Disorders and Stroke. Dr. Story Landis has been Director since September 2003. Dr. Landis received her undergraduate degree in biology from Wellesley and her master's and Ph.D. from Harvard.

Dr. Landis, welcome and please proceed.

STATEMENT OF STORY LANDIS, Ph.D., DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

Dr. LANDIS. Thank you very much. I, like my colleagues, am delighted to have this opportunity to be able to testify today about research on mind, brain, and behavior. As I have heard from each of us, disorders of brain function are leading causes of disability in the modern age, and I think that Dr. Batte did a very good job of pointing out some of the issues.

NINDS is responsible for reducing the burden of several hundred neurological disorders. These range from very common disorders,

like stroke, Parkinson's, epilepsy, to relatively rare but individually devastating disorders like ALS—amyotrophic lateral sclerosis—and spinal muscular atrophy. So in addition to the burden in terms of lost life, disability and suffering, neurological diseases cause billions of dollars each year in medical expenses and reduced productivity.

Neurological disorders affect people of all ages. We have increasing disability in children as a growing problem because of brain injury in premature infants who now survive when they would not have before. As Americans live longer lives, age-related disorders like dementia, stroke, Parkinson's, and epilepsy are increasing in incidence. Meeting the challenge of neurological disorders therefore has never been more important. The good news is that the advances in basic and clinical neuroscience provide enormous opportunities.

Now, 20 years ago neurology was really regarded as a diagnostic discipline because neurologists had relatively few therapies to offer patients. They could tell you what the lesion was, but they could not necessarily do anything about it. Through NINDS-funded research we have actually made extraordinary progress. For example, there used to be only a handful of drugs to treat epilepsy and now we have more than 20. Steroids used to be the only treatment for multiple sclerosis, but now there are three FDA-approved drugs and more in the pipeline. Deep brain stimulation (DBS) dramatically helps many people with Parkinson's disease who are no longer benefited by medicines. Turn off the stimulator and they are frozen, unable to walk. Turn on the stimulator and in the best cases, the ones that make it to "Dateline", they can dance.

Now, while DBS is very exciting, it, like other treatments for Parkinson's disease, addresses the symptoms but not the underlying causes. The underlying cause is death of brain cells. So we need desperately to figure out treatments that will protect the neurons that remain. Just last week, NINDS began to enroll patients in large phase 3 clinical trials to determine whether we can slow the loss of brain cells and prevent the slow decline of patients with Parkinson's. We hope to begin a second trial of a neuroprotective agent soon.

As you or someone else alluded to, even just the small change in the rate of progression of any of these chronic neurodegenerative diseases would make a very big difference in the quality of life and how people fared.

Now, the scientific rationale for the two drugs that we are studying in these neuroprotective trials is strong or else we would not be funding them. But we really believe, because of the discovery of eight genes that cause familial Parkinson's disease and our ability to understand how the proteins that those genes encode for, we should have much better and more targeted drugs soon, and we would then put these drugs into neuroprotective trials that would prevent neuron loss.

So I would like to talk a little bit about stroke. NINDS is the lead Institute for stroke. It is in our name. Stroke is the third leading cause of death and disability in the United States. The good news is that CDC data demonstrate that age-adjusted stroke deaths have declined from 180 per 100,000 in 1950 to 50 in 2004.

That is age-adjusted, though. So the bad news is actually that because our population is aging we are barely keeping pace in terms of incidence of stroke.

NINDS has three strategies for stroke. First is prevention, then minimizing damage when a stroke occurs, and finally developing better strategies for recovery. In terms of prevention, the most important thing is to know what increases your risk of a stroke. NINDS has a number of epidemiological studies that look at that. The largest of these is called REGARDS which has recruited over 30,000 people, half of them African American, many in the stroke belt. The goal is to study how race and geography influence the incidence of stroke.

Now, there are already two important findings in this study. The first is that there are many more silent strokes—that is a stroke that does not take someone to the hospital or give you an obvious disability—than anybody expected, particularly in the middle aged population. The second is that, while we have always thought of hypertension as the principal risk factor for stroke, we now, based on this REGARDS study, understand that diabetes is also very important. So obviously NINDS not only needs to partner with NHLBI and the American Heart Association for reducing hypertension, but we also need to look at partnering with NIDDK and diabetes groups for reducing diabetes.

DIABETES AND STROKE

Senator HARKIN. Excuse me for interrupting at this point. Are you saying that diabetes is a leading indicator for having a stroke?

Dr. LANDIS. In this population, being diabetic significantly increases your risk of having a stroke.

Senator HARKIN. In this population.

Dr. LANDIS. In this population of 30,000 people, many of them who are not patients yet. We did not expect that but we knew about hypertension and not about diabetes. This is not surprising. Diabetics are often overweight and do not exercise so it is not surprising, but it had not actually been demonstrated.

Senator HARKIN. I am just curious again to take this a step further. Okay, diabetic, but then have you screened all those to look at what has been their cholesterol levels, all the other factors?

Dr. LANDIS. This has been a recent study, 4 years old, and we are just beginning to see the fruits of these initial analyses of data. So the first publications are just beginning to come out and we are in the process now of accepting an application to refund the study. Obviously, the more things that we could look at, the better data we would get in terms of identifying risk factors and being able then to think about interventions.

So if prevention fails, obviously we want to minimize damage when someone has a stroke. The NINDS Institute a decade ago had a clinical trial that showed that the clot-busting drug, TPA, could restore blood flow to the brain and prevent brain damage if it was given within 3 hours of stroke onset. I can tell you very honestly that this transformed acute stroke care in this country. You did not get shuttled off to a dark room and given an aspirin. You actually got aggressively treated. I think it has been a model for how other neurological diseases can be treated.

Now, this treatment really benefits patients, obviously. A third of the patients who get this treatment leave the hospital with no sequelae whatsoever. It reduces long-term disability-related costs and there is a net savings of more than \$4 million for each 100 patients treated because you do not have to do long-term care and rehabilitation.

We are currently running clinical trials to boost the effectiveness of TPA, to select patients who might benefit beyond the current 3-hour limit, and to determine whether if you inject the TPA into the blocked brain artery you get more benefit than if you just do it intravenously.

Now, if you have a stroke, we need to help people recover from it. Because of animal studies, we know that there is remarkable plasticity in the adult brain. Because of that plasticity, investigators that were funded both by NINDS and NICHD forced stroke patients to use the affected arm and this stimulated the formation of new brain connections, and a 2-week study of rehabilitation based on this insight showed lasting clinical improvement in arm function for stroke survivors.

So it is very clear that increasing the brain's latent capacity to rewire and/or repair itself is an extremely exciting area for research in NINDS, and will also impact many other brain disorders.

I want to, in closing, underscore two points that were made by the panel of outside scientists at last week's hearing. I thought they were very impressive. I watched it on C-SPAN. The first is we need to encourage new ideas and new investigators. You go to any scientific meeting and most of the people in the audience, who are speaking and presenting have grey hair and, while they will make advances—I mean no offense to the grey hair because I have it myself—they will make advances over the next decade, but we will not cure many of our diseases. We will improve treatment, but not cure them in the next 10 years so that is a very important issue.

The second is the importance of NIH basic research, both for the public health of the Nation and the competitiveness of our private sector. Now, while each of the institutes that we represent has a distinct mission, the structure requires that we answer fundamental and shared questions about the brain, such as how genes and the environment shape the brain and how the brain represents thoughts, emotions, memories, sounds, and leads to behavior. Answers to these questions are key to preventing all kinds of brain diseases, as well as learning how to optimize brain health and help all our citizens realize their full potential.

PREPARED STATEMENT

So recognizing that we share the brain and the significant synergy that will come from collaboration, the institutes represented here along with others who will testify in different hearings created the Neuroscience Blueprint for the extramural community and the Porter Neuroscience building in the intramural program, which I would say is not completed. We would be pleased to tell you more about the blueprint and the Porter building during the question period.

I would like to thank you very much for your attention and your support.

[The statement follows:]

PREPARED STATEMENT OF DR. STORY C. LANDIS

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2008 President's budget request for NINDS. The mission of NINDS is to reduce the burden of neurological disorders by developing ways to prevent or to treat these diseases. The fiscal year 2008 budget is \$1,537,019,000.

Disorders of the nervous system, common and rare, affect people of all ages. They cause an enormous burden in lost life, disability, and suffering, as well as billions of dollars each year in medical expenses and reduced productivity. Because Americans are living longer, stroke, dementias, Parkinson's disease, epilepsy, and other neurological disorders that rise in frequency with age are increasing. Abnormalities in nervous system development rob many children of a normal life. As more premature infants survive through intensive care, neurological disability in children is a growing problem. Many people, often young adults, now survive trauma to the spinal cord or brain, but confront a lifetime of disability. Meeting the challenge of neurological disorders has never been more important, but the opportunities for progress have never been greater. Advances in neuroscience are transforming the practice of neurology from diagnosing patients, with only inadequate treatments to offer, to intervening to stop or prevent disease, with treatments tailored to each person. Neurosurgery is likewise increasingly capable of preventing or repairing damage to the brain.

IMPACT OF CLINICAL RESEARCH

NINDS has its most immediate impact on public health through phase III clinical trials, which test the safety and efficacy of interventions. It is essential to assess the return on this investment in improving quality of life. At the request of the National Advisory Neurological Disorders and Stroke Council, the institute contracted for an independent evaluation of the costs and benefits of all NINDS phase III clinical trials conducted from 1977 to 2000 [The Lancet 367:1319-27, 2006]. The total cost of the clinical trials in the study was \$335 million (adjusted to 2004 dollars). Over 10 years, the benefits exceeded \$15 billion and added 470,000 healthy years of life to people in the United States. For the entire period of the study, the benefits surpassed \$50 billion, which was greater than the total NINDS budget over that period (\$29.5 billion). Advances in neuroscience are yielding more clinical trial opportunities than ever before, but trials are expensive and take years to complete. NINDS is developing computer models to estimate in advance which trials would have the most impact on public health.

TRANSLATING PROMISE INTO PROGRESS

Because of progress over the last decades, thousands of strokes are prevented each year and emergency treatment lessens chronic disability for many people who do have a stroke. Data this year from the Centers for Disease Control and Prevention (CDC) show that age-adjusted stroke deaths are continuing to decline, from 65.3/100,000 in 1990 to 50.0/100,000 in 2004, compared with 180/100,000 in 1950. Better surgical treatments and drugs also help people who have chronic pain, dystonia, epilepsy, migraine, multiple sclerosis, neuropathies, Parkinson's disease, and many other diseases. Brain imaging has revolutionized neurology and neurosurgery. For many people, genetic testing eliminates arduous and expensive diagnostic odysseys to determine which of the hundreds of neurological disorders is responsible for their problems. NIH research drives this progress.

A decade ago an NINDS clinical trial showed that the clot busting drug tPA was the first emergency treatment that could improve the outcome from stroke. This engaged the community in stroke education, stimulated the organization of more than 250 certified primary stroke centers nationally, and energized researchers to develop even better emergency care. In the future, combinations of tPA and neuroprotective therapies will rescue brain tissue from permanent damage, and rapid diagnosis will identify which patients will benefit from what interventions while the critical time window for intervention is still open. This year NINDS investigators showed how MRI brain imaging can improve diagnosis for patients who come into emergency rooms with suspected strokes, and other scientists are developing rapid blood tests for stroke using genomic fingerprinting. Several strategies to boost tPA's effectiveness are in development, including clinical trials of ultrasound to help break clots quickly, and direct injection of tPA through a catheter threaded into the blocked brain artery for patients with large clots that are difficult to clear. Clinical trials of interventions, studies of risk factors, and gene studies will also continue the mo-

mentum of stroke prevention, with increasingly personalized guidance. This year, to illustrate that trend, NINDS-funded researchers discovered a gene variation, more common in African-Americans, that predisposes young women who smoke to have strokes.

For people who do have a stroke, neuroscience is offering new approaches to recover lost functions. New understanding of brain plasticity suggested that, counter to intuition, forcing patients to use an affected arm would stimulate adaptive changes in the brain. A two week behavioral rehabilitation regimen based on this insight yielded lasting clinical improvements for stroke survivors who had chronic weakness in one arm. Studies are building on this strategy, using behavioral methods, drugs, and brain stimulators to engage the brains' natural capacity to adapt, and even generate new brain cells. Enhancing the brain's latent capacity to repair itself may also help people recover from traumatic brain injury and many other disorders.

A decade ago, spinal muscular atrophy (SMA) was one of hundreds of poorly understood inherited disorders that affect the nervous system, and the outlook for developing treatments was bleak. The discovery of the gene defect that causes SMA revealed a rational strategy for developing drug therapy. In just a few years, the NINDS SMA Project developed a detailed drug development plan and tested hundreds of new compounds in laboratory tests. Most recently, some of these potential drugs increased the amount of the critical missing protein to normal levels in cultured cells from patients who have SMA. The SMA Project is testing the effectiveness of these compounds in animals with SMA and assessing their safety to bring these potential drugs to clinical trials, offering significant promise for helping people who have SMA.

Research on SMA illustrates the path from gene to understanding to treatment. Researchers have now characterized well over 200 mutations that cause neurological disorders. For inherited ataxias, Batten disease, Down syndrome, Huntington's disease, muscular dystrophy, Rett syndrome, neurofibromatosis, and many other previously baffling disorders, researchers have genetically engineered animals that mimic the human disorder and then replaced genes, turned harmful genes off, turned up compensatory genes, or counteracted gene defects with drugs that target the affected cellular functions. In the future, application of these strategies to patients could preempt or even reverse the damage caused by gene defects. NINDS is aggressively pursuing opportunities to translate science advances such as these to treatments.

The goal for epilepsy is "no seizures, no side effects," or better yet, to prevent epilepsy from developing. In the 1960's only a handful of drugs were available to treat epilepsy. Today there are more than 20, which control seizures in about two-thirds of people who have epilepsy. Ten were developed with special programs at the NIH, and the NINDS Anticonvulsant Screening Program continues to catalyze academic and industry efforts. New animal models will allow screening potential drugs for people who have treatment-resistant epilepsy and for blocking epilepsy development. Clinical trials are now testing interventions to prevent epilepsy after head trauma, a major risk factor. Gene studies, now underway, will enable physicians to personalize treatment, choosing the best drugs or other therapies for each person with epilepsy, avoiding the current trial and error process.

Drugs that are the mainstay of Parkinson's disease treatment mask symptoms but ultimately fail because they do not slow the underlying neurodegeneration. Deep brain stimulation (DBS) dramatically helps many people with advanced Parkinson's disease. NIH research, from technology development to clinical trials, is improving DBS and expanding its use for other neurological and psychiatric diseases. Researchers are also developing drugs to slow neurodegeneration itself. NINDS assessed candidate neuroprotective drugs for Parkinson's disease, conducted early phase clinical trials, and is beginning a large clinical trial of a neuroprotective drug. Even a modest slowing of Parkinson's or other neurodegenerative diseases would have an immense impact on public health, so drugs to forestall neurodegeneration are a high priority.

Stem cell research has captured the public's attention. Research on animals with Parkinson's-like disease illustrates the promise and challenge of stem cell therapy. In recent tests, stem cell-derived transplants dramatically improved movement, but also produced tumors in some animals. Stem cell therapies for spinal cord injury, muscular dystrophy, and many other neurological disorders continue to advance toward the clinic. However, better control of stem cells is necessary before these therapies are ready for people, so understanding the basic biology of stem cells is essential.

Scientists are also making progress in answering fundamental mysteries, such as how genes and the environment shape the brain and how the brain represents

thoughts, emotions, and memories. Answering basic questions such as these is the key to not only treating disease, but knowing how people can maintain a healthy brain and realize their full potential at every age.

PLANNING FOR THE FUTURE

NINDS continuously monitors research needs and opportunities. The institute recently posted a mid-course review of the Stroke Progress Review Group and a new plan for Parkinson's disease. An epilepsy conference this month will follow up the meeting that launched the epilepsy benchmarks planning process. More broadly, NINDS is beginning a process to update its strategic plan. With input from all stakeholders, we will identify aspirational goals that will guide us to best achieve our mission and then focus on what steps NINDS can take to realize this vision. In order to achieve our paramount goal of reducing the burden of neurological disorders, we must certainly continue to support young scientists, to engage the ingenuity of the scientific and medical community, to work with the private sector, and to collaborate with other components of the NIH, as we now do through the NIH Roadmap, the NIH Blueprint for Neuroscience, working groups on specific diseases, as well as dozens of specific inter-institute initiatives.

Thank you, Mr. Chairman. I would be pleased answer questions from the Committee.

Senator HARKIN. Dr. Landis, thank you very much.

Let me—I have got quite a few questions here. First of all, talk to me about something that you mentioned in your written statement. I am hearing more and more about the debilitating effects of migraine headache.

Dr. LANDIS. Right.

MIGRAINE HEADACHES

Senator HARKIN. I saw some figures, I cannot repeat them here because I do not have them here, but just how prevalent migraine headaches are. More and more I am meeting people who have migraine headaches. I have had some people who have worked for me in the past who have had them and it is just very debilitating.

So what is happening? Why? What is the story?

Dr. LANDIS. It is not completely clear. What is completely clear is that there are several different causes of migraine headaches and that if you have mutations in particular kinds of ion channels you can have migraine, and that it can be a spreading depression. We have, fortunately, over the past decade developed a number of treatments which can forestall a migraine once it begins. We also have learned in some cases that long-term treatment with calcium channel blockers can prevent migraines.

We do not know as much as we should. It is an area that has not received as much attention as it might. NINDS recently released a request for applications specifically in the area of migraine headaches. We recognize it is an underserved area and hope to stimulate research in it.

Senator HARKIN. I do not know whether I am just hearing more about it now and finding more people. Is it increasing in prevalence?

Dr. LANDIS. I do not think it is increasing. I think people are more attentive to it than they have been before. One of the problems with being an Institute like NINDS is making choices between stroke and Parkinson's and migraine. We are hoping in our planning process to undertake over the next 2 years, a look across all the diseases that we are responsible for and see the ones that we have perhaps not invested in as much as we might.

Senator HARKIN. One disease that you know that I have been interested in, I did not even know about it until a few years ago, but the more I have looked at it the more I have seen what you have been doing at the Institute on it. It seems to me that you are making great progress in understanding spinal muscular atrophy, which I had not heard of until a few years ago. I have met with some people in my home State with children who have that and others.

The more I have learned about it, the more I think that there may be in this research area applicability to other diseases. You have identified the gene, I think.

Dr. LANDIS. We did not, but it has been identified.

Senator HARKIN. It has been identified. Somebody did.

Dr. LANDIS. Right. The Europeans actually, I think.

SPINAL MUSCULAR ATROPHY

Senator HARKIN. Oh, is that right? Sorry to hear that. But that is all right.

Tell me about the progress on spinal muscular atrophy, because I keep hearing that this has some connectivity to other types of diseases.

Dr. LANDIS. There are two pieces of our investment in research in spinal muscular atrophy that I think are important. The first was the Institute decided a number of years ago that we would try an experiment, which was to identify a particular disease, a devastating disease. In SMA, kids lose their motor neurons, and in babies many of them die within the first year. Some of them die within 4 to 5 years depending on the type. We would try to identify a particular disease which was amenable to a concentrated investment, a focused effort in therapeutics development.

After a survey of many of the diseases that we were responsible for, SMA emerged as the likeliest candidate for this experiment. Mutation occurs in the SMN-1 gene. There is a second gene, SMN-2, which codes for the same protein, but does it much less effectively. We had compounds which we knew could increase the levels of SMN, Survival of Motor Neuron protein. So we put a big chunk of money, \$20 million, into a contract to actually come up with at least one drug that would have an investigational new drug designation within 4 years, or the end of 2007. We are not going to make the end of 2007 because it turned out that what we had to do is actually create a virtual biotechnology company through this contract.

But we are making significant progress. We recently filed a patent for one chemical backbone and have a number of compounds in there which cross the blood-brain barrier which significantly increase the amount of SMN protein. We are taking those compounds to animal studies to see which is the most effective in increasing the survival of these animals.

So it is an experiment for the Institute to see if we can actually push forward therapeutics in a very significant way and make a difference. Then the other issue is that these are the same neurons that die in ALS. The kinds of things that might promote survival of motor neurons in SMA might also be instructive for ALS. The mechanism—the failure to make a splice—again a technical term—

is apparent in a number of other diseases we are responsible for. If we can figure out a way to make the splice work, we might use that same strategy in other diseases.

So it has a number of very interesting implications for the Institute in how we manage rare diseases and how we move from one rare disease to another.

STROKE

Senator HARKIN. You mentioned that deaths have declined due to stroke, but I just wonder about the incidence of stroke. I do not think the instance of stroke is down.

Dr. LANDIS. No. Age-corrected deaths due to stroke have decreased. The incidence is not decreasing because our population is aging.

Senator HARKIN. Well, also I think we have better interventions, too, for stroke.

Dr. LANDIS. Right.

Senator HARKIN. I think stroke remains still one of the feared things that can happen to someone. They are just so unexpected and can happen to anyone at any time. It is that early intervention if you can get to it right away that helps, if you get that—

Dr. LANDIS. TPA.

Senator HARKIN. What is it called? TPA.

Dr. LANDIS. Tissue Plasminogen Activator.

Senator HARKIN. TPA.

Dr. LANDIS. TPA.

Senator HARKIN. I am also interested in Parkinson's disease. In your testimony you talked about deep brain stimulation for Parkinson's disease. Again, how much progress is being made in this?

Dr. LANDIS. We are presently conducting with the Veterans Administration a clinical trial to determine whether deep brain stimulation is better than best medical treatment. A group in Europe has already produced some data that are consistent with that, but we want to make sure that that is in fact true.

The second issue is where do you put the stimulating electrode. So some people, some surgeons, put it in something called the GPI and others put it in the STN, and we do not know which locus is better. So the second part of this NINDS-VA study is to determine where is the best place to put it.

One of the most surprising things is that deep brain stimulation actually works for a number of other neurological diseases—dystonia, Tourette's—and has shown to have benefit for chronic untreatable depression. So the notion of putting stimulating electrodes in the brain and altering patterns of brain activity may be applicable to more than just neurological diseases.

TRANS-CRANIAL MAGNETIC STIMULATION

Senator HARKIN. A year ago or so maybe, I was visiting my office. A friend of mine brought a person in, a woman who had been to Greece—she had Parkinson's disease—to undergo some new therapies. The way she described it to me, she had pictures of it. It was some doctors in Greece, some scientists, had developed like a helmet they put over her head, but it did not penetrate the skull, but it was like—

Dr. LANDIS. Trans-cranial magnetic stimulation probably.

Senator HARKIN. Thank you. I had no idea. Probably so if you say so.

Dr. LANDIS. Well, that is a strategy that we are looking at in this country as well.

Senator HARKIN. This woman came back, and it did not cure her of Parkinson's, but it really alleviated the symptoms greatly for her. So I do not know if you are looking at anything like that.

Dr. LANDIS. Obviously, if you could get changes in activity, circuitry, without having to stick electrodes in the brain, that would be preferable. NINDS and the Department of Defense are exploring the use of trans-cranial magnetic stimulation as an alternative to deep brain stimulation.

Now, the problem with deep brain stimulation is it does not stop neuron cell death. I think Dr. Fischbach when he testified and said that we would have a cure for Parkinson's in 5 or maybe 10 years actually really believed in his heart that the change in activity from deep brain stimulation would promote survival of neurons in Parkinson's, and that has been a disappointment. It has not done that. But it does provide symptomatic relief.

POST-TRAUMATIC STRESS DISORDER

Senator HARKIN. Dr. Insel, I have been told that 1 out of every 3 returning Iraqi veterans—this is sort of a follow-up on what Senator Specter asked—1 out of 3 seeks mental health help some time during the first year. Now, whether that is 1 out of 3 or 1 out of 4, it is very high. That is just those who actually seek it. What about those that do not? How many more out there that are trying to tough it out?

Any thoughts on why it is so prevalent and why these returning vets are having mental health problems and why the incidence? It seems to me—now, maybe I am wrong, but the incidence of post-traumatic stress disorder is going up, and sometimes PTSD does not exhibit itself for months afterward, 5 months, 6 months, 7 months afterward.

Talk to me a little bit more about post-traumatic stress disorder. What is it? Is it more prevalent now than in the past? How about all these returning veterans who are having mental health problems? Is this more than any war in the past? Do we know? Maybe we do not even know that. I do not know.

Dr. INSEL. We do not know yet. Post-traumatic stress disorder plays out over many, many months and sometimes years. We often now think about post-traumatic stress disorder as a failure of recovery. Everyone after a traumatic event is, in lay terms, shell-shocked. They have symptoms. They have trouble sleeping. They may be preoccupied by the event. They have a need to talk about it all the time. We would all feel negative impactly if the event is traumatic enough, and it does not have to be combat. It could be a car accident. We have all experienced this.

Most people can talk it through and recover and 6 months later, it is a distant memory. They are able to sleep and not use alcohol or illicit drugs to cope with this. For some reason, and it is not due necessarily to the degree of trauma. It has more to do with the individual vulnerability to traumatic events and their psychological

sequelae. Some people do not recover in the way that most of us do. Those are the people who develop PTSD. The numbers range from 13 to 16 percent in the current war. In the Vietnam War the numbers were higher. But that is over a longer period of time.

We will have to see. The assumption would be that if the numbers are 13 percent now—and as I mentioned before, that equates to about 170,000 affected individuals. One would think that they will go up even further over the next year or so. Often the way it happens is that people are coping well enough until there is a second hit. They watch a movie that reminds them of the trauma. They have a loss in their life. They have some stressor that then tips the balance, and they then emerge with full-blown symptoms.

Senator HARKIN. Of course, your institute is actively doing research in post-traumatic stress disorder?

Dr. INSEL. Absolutely. We have decided through much of this effort to collaborate with DOD and with the VA. So we have a large effort. Actually we have a joint RFA, a request for applications, that has been funded, where we have half the grants and they have the other half. We work together with them because this is where we think the need is greatest.

Where we would really like to go with this is to understand this individual pattern of vulnerability, to identify who needs the early intervention, before the point where someone develops all of the secondary aspects of PTSD, the depression, the alcohol abuse, the substance abuse, and at that point preempt all of that by being able to get to them early.

NIMH BUDGET

Senator HARKIN. Your Institute's budget for next year is \$1.4 billion.

Dr. INSEL. Right.

BASIC NEUROSCIENCE

Senator HARKIN. What would be the largest sector where that money would go for research?

Dr. INSEL. The single largest—we have five research divisions and the largest one of them is in the basic neuroscience arena. We really are trying to get at the question you asked before, actually the critical question, understanding the pathophysiology of these illnesses. It is not just a matter of tweaking the drugs that we have now and figuring out how to use them best. That is important, but we want to get to a point where we have a new generation of compounds that we can think of as either preventive interventions or cures, really raising the bar on what we expect for interventions. That is going to require having a much better fundamental understanding at the level of molecules and cells and brain systems about how something goes wrong to give you the psychosis of schizophrenia, the hopelessness of depression, the symptoms of PTSD. We do not know that. We know a little bit about how to treat them, but we need to know a lot more of the fundamentals.

That has been our biggest effort.

STRESS

Senator HARKIN. Dr. Insel, would you be the proper person that I would ask this question of? I am going to ask it, but maybe it is another Institute. I do not know. The effect that stress plays in diseases. I have read a lot about in science magazines and other things that more and more the high factor of stress, both in perhaps getting a disease, but in the generation of that disease after you get it and how it progresses, that stress is an indicator for how ill you might become.

So are you looking at stress? Is this part of your \$1.4 billion, looking at stress and how stress levels affect a person's ability to ward off diseases and illnesses or become more susceptible because they have a higher level of stress? Is that you or is that somebody else?

Dr. INSEL. That is a number of us. Dr. Volkow talked about that at great length and her specific interest is on developmental stress and how it can tease up an individual to be responsive later with pathological behaviors like addiction. NIMH has a similar interest, but it is more focused on depression, where we know that children who have been stressed, particularly at certain vulnerable times in development, are at much, much greater risk for depression after puberty or even into young adulthood.

The mechanism by which that happens is where our interest now is taking us. We want to know, what is it about stress that affects one individual to make them subsequently very depressed or drug addicted and the next individual takes the same event and they somehow get immunized, they get stronger from having been challenged in some way. We do not know enough to understand those individual differences.

So that is where a lot of our effort is going, finding again the molecular and cellular substrates of how stress affects the brain is we think one of the ways to get there.

Senator HARKIN. But you are—somewhere in this whole big \$1.4 billion, you do have research on stress that is ongoing, dealing with how stress relates to physiological problems?

Dr. INSEL. Absolutely. It is a big part of our effort in terms of mechanisms, understanding mechanisms, and a lot of that is going on in animal research, where we can really control many of the variables and look specifically at what stress is doing. Dr. Volkow can tell you about some of the work they are doing as well in looking at the long-term effects of stress.

GENETIC FACTORS FOR ADDICTION

Senator HARKIN. I was going to ask Dr. Volkow about that. Oh, yes, I know. You were talking about the environmental factors to drug abuse, but you said that genes—I wrote this down because it really sounded almost too neat—50 percent of the factors are genetic for addiction.

Dr. VOLKOW. Correct.

Senator HARKIN. You really hold that it is 50 percent?

Dr. VOLKOW. 50 percent, and actually this is very consistent and reproducible. The vulnerabilities for becoming addicted is at least 50 percent, analytically determined. The other 50 percent is your

environmental factors involved with it. You know, with animal experiments what we are trying to do, of course, is identify which genes make you vulnerable. We have come to recognize that there are going to be genes that make you vulnerable to experiment with drugs which are going to be different from those genes that are going to make you vulnerable—if you get repeated exposure, you may or may not become addicted. Approximately 10 percent of people will. Those genes that we identified evidently are linked with the process of plasticity and also involving learning and memory.

So it appears that for you to have the vulnerability, you have the genes that will be much more likely to be modified by environmental exposure to drugs to create new connections, but then are likely to be driving the compulsive intake of drugs.

STRESS AND ADDICTION

Senator HARKIN. Following up on that, it would seem that stress does play a high part, a big part, in people getting addicted to drugs, to relieve stress or they get stressed out. They want to smoke or they want to drink or they want to—

Dr. VOLKOW. Take marijuana.

Senator HARKIN [continuing]. Take marijuana or more serious drugs.

Dr. VOLKOW. Yes, and we are very much interested, and we have from the perspective of basic science, we have known for many years with the epidemiological data that environmental stressors, and in particular social stressors are some of the most profound in human subjects. We are very, very sensitive to social stressors. We have known that they affect our vulnerability to addiction. It is clear when people are in war, for example, which is very stressful, drug abuse can go up in a way to cope with the stress. Or if you come up with an environment where you have been physically abused or sexually abused, more likely to take drugs.

What we did not know is why and what is the social stressor doing to your brain that makes you more vulnerable. For example, there have been studies now both in rodents and in primates that show that social hierarchical structure and pending on the level, if you are dominant versus subordinate, can modify specific proteins that regulate, modulate your vulnerability to take drugs.

So if you are in an environment and very subordinate in a system that is very stressful to be a subordinate, then those proteins go down and that leads you to a facilitation of taking drugs. That is what I was highlighting. Of course, the challenge now is how can we buffer. If someone is born into that environment, if we learn how does that stress produce those changes, how can we buffer an intervention to be able to rehabilitate, to go back to recover some of those changes that is the basic perspective.

We are also very interested in the mean time to do interventions and to evaluate the extent to which specific prevention interventions are useful. For example, we take for granted social skills. A child that has poor social skills predicts higher likelihood that they will take drugs. So something that makes a lot of sense, intuitive sense. Why do we not as a prevention strategy identify those kids that are unable to negotiate interactions with their peers as a pre-

vention effort? It will be beneficial not just for drug use, but also for mental illness.

So that is the sort of thing that we are also encouraging from the prevention behavioral intervention.

HEAD START

Senator HARKIN. That is what the Head Start program is for. Yet Head Start I think gets about half of the eligible preschoolers now. By the way, Head Start is not an educational program; it is a social skills program with education added in. A lot of people think Head Start is education. It is not that. That is why it is in the Department of Health and Human Services, not in the Department of Education. I do not know why I am telling you all this, but anyway.

But the idea was to give these kids that kind of social interaction and that type of thing. But the problem is that we do not pay Head Start teachers well enough. We do not get qualified, a lot of qualified people in there with Head Start.

So anyway, it just goes back to what you say about getting those early interventions.

Dr. VOLKOW. Correct.

Senator HARKIN. Which we know are predictors for drug abuse and for mental health problems and for drug abuse.

Dr. VOLKOW. Also can, for example, prevent criminal behavior, which is something that of course we just hinted at.

NIH BLUEPRINT

Senator HARKIN. Well, that is for a different thing.

One last question and this is for all of you. All the Institutes here today have been involved in a collaborative effort called the NIH Blueprint for Neuroscience Research. Dr. Landis, I will start with you and we will just go down. What is this effort? What has been achieved? What are you doing, and what are the plans for next year, and how do you all participate and kick into this? So just tell me about the NIH Blueprint for Neuroscience Research so I can better understand it.

Dr. LANDIS. A number of years ago we recognized that Institutes which funded research in the neurosciences had common interests, common goals, and common needs, and set out to actually create a collaborative environment. Once a month all the Institute Directors or Center Directors participate in this meet to discuss important initiatives, fund workshops and requests for applications and share best practices.

We have a modest budget. Each of us chips in money to a central pot that represents a fraction, a very small fraction, of the amount of money from our budget that funds neuroscience. We discuss as a group what are the most important and the most interesting ways we can spend that money. We have funded training programs that benefit all the institutes. We have funded the generation of mutant mice which benefit all the Institutes.

Several years ago we thought, instead of just investing in tools, that we might want to invest in some science. We picked three themes, neural degeneration, neural development, and plasticity, and have been working through those themes once a year. I have

to say, you know, it is pretty amazing that we can get each of the Institute Directors to show up once a month to talk about science and initiatives, but we have done it. I think all the institutes in the neurosciences are a lot stronger for having done this.

I am sure this is a little like an elephant, where I have just given you the trunk, someone else might give you a leg.

Senator HARKIN. Are you a leg, or what are you?

Dr. LANDIS. He is the ear.

Senator HARKIN. Oh, he is the ear, of course.

Dr. BATTEY. There is not a lot I can add to Story's beautiful description of the blueprint, other than to maybe make two observations. We were talking earlier about *Math-1* and the mouse knock-out that led us to the discovery that it was essential for hair cell development. That was not my grantee. That was her grantee [indicating], Louis Ogbee in Texas, did that.

Dr. LANDIS. He actually was picking up on a gene discovered in *drosophila* that is required for the development of a particular kind of external sensory neurons, and he said, gee, why do we not figure out what it does in mammals.

Dr. BATTEY. So my point is that the neuroscience Institutes have remarkable overlap in the experiments that need to be done to move this forward. We also have remarkable overlap in the needs. For example, Story has mentioned many times neuronal degeneration and I have told about hair cell degeneration. It is almost certain that many of the mechanisms that underlie degeneration of neurons are going to be the same ones that are going to be involved in degeneration of hair cells.

So by pooling our resources and generating common reagents and resources, we leverage each other's science and advance the science of my relatively modest sized Institute is advanced enormously by the discoveries made in mental health, neurology, and the other neuroscience Institutes.

So in particular for the smaller Institutes, the blueprint has been a really wonderful thing.

Senator HARKIN. Anybody else? Dr. Volkow, Dr. Li?

Dr. LI. I would echo what Dr. Battey said. The NIAAA being a small Institute, we benefit tremendously from this collaboration, especially when it comes to not only just providing resources, but in having projects that are of joint interest, such as neural degeneration, neural development, and neural plasticity. This is the value of it.

Dr. VOLKOW. I think I want to commend the notion that the big frontier after the genome is to understand how the human brain works, which is extraordinarily complex. We now have extraordinary tools to actually look inside the human brain, and not just look at its morphology but how it functions. So this has given us an opportunity, all of us together, to invest resources to understand how, for example, the brain changes as a function of development, something that would have been extraordinarily costly for one single institute. By putting our funding together, we can start to get the standardized data set that any investigator outside can go in to query, and that gives us the perspective to start with, for example how does the brain change as we grow from childhood to ado-

lescence to adulthood. This is just an example about how powerful it is to integrate our efforts.

Dr. INSEL. I know we are going to be having to stop in a moment, so I would say that in terms of both the Neuroscience Blueprint and everything else that you have heard for the last almost 2 hours, we could not have done any of this without your support and the support of Senator Specter when he served as chair. I think I speak for all of us to say how grateful we are for all that you have done on our behalf.

We are entirely committed to making a difference for the American people, but we only do it because you are there to help us along. We are delighted to have a chance to tell you a little bit about, and this is really a very little bit, about what all of us have been involved with. But most of all, we want to say thank you for being such a leader for us in this regard.

Senator HARKIN. You are very kind, Dr. Insel, but I will not let you have the last word on that.

I want to thank all of you. It has been very enlightening. I enjoy this kind of a setting. I just learn things. I think it is very helpful to have this kind of a discussion among the institutes over at least a couple hour period of time. We will be continuing this process with other institutes.

But in that regard of what you were just saying, Dr. Insel, let me return the favor and the compliment by thanking each one of you, each one of you, for a lifetime of dedication to research, to science, to doing the things that help to try to improve our quality of life and the way people live, to cure illnesses and diseases, to help people who may be at rope's end, and especially in mental health. They just have nowhere to go and they do not know what to do. You have been making great progress in these areas, all these areas. There is great hope out there for all of the things we have done, the genetics and stem cells, with new interventions coming on, some of the things that you talked about, Dr. Landis. Of course, you know of my intense interest in deafness and communications disorders. We are making significant progress in areas, although I want to move faster, as you can imagine.

Dr. BATTEY. So do I.

Senator HARKIN. I know you do, Dr. Battey.

Alcoholism, drug abuse, again all these areas.

I just close by saying thank you. I thank each of you. I just hope that young people today will look upon each one of you as role models, as something to aspire to, to get involved in research, to get involved in science, to take it up as life work, and to think about the good that they can do during a lifetime of service.

What we do at NIH, what each of you do, leaves a legacy that just cannot be expressed in monetary terms. It can only be expressed in terms of people's lives and how much better kids are today and how much better their lives are. To me it is just the best work that I can imagine anyone doing. I hope that we have another generation of Dr. Insel's and Volkow's and Li's and Battey's and Landis's coming along.

That is my way of saying thank you very much, and I look forward to continuing our discussions and information that you would have for the subcommittee at any time. We will be doing our budg-

et, getting our things worked out. But I think you have a lot of support here and I know that Senator Specter and I have worked together on this now for, we are going on almost 20 years together on this committee. We have a great partnership. I could not ask for a better friend and partner. Whether he is chairman or I am chairman, it has not made a lick of difference. I just hope that we will have the finances and the budget and the money in order to help you do your work and to encourage these younger scientists coming along to know that this is something that they can dedicate their lives to and that they will be able to get the funding that will enable them to do their research and to do their work.

It is going to be very tough. It is going to be very tough. I remember when I was a kid watching—it is funny I would think of this right now, but we used to watch GE Theater on television and the host was Ronald Reagan. I remember GE's theme at that time was "At General Electric Research Is Our Most Important Product." I think that is what we have got to be about here. Research is our most important product, and you do it well.

ADDITIONAL COMMITTEE QUESTIONS

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

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

QUESTIONS SUBMITTED BY SENATOR TOM HARKIN

CLINICAL TRIALS NETWORK AND NIMH

Question. Dr. Insel, I understand that the large clinical trials that NIMH has undertaken in recent years (CATIE on schizophrenia, STEP-BD on bipolar disorder, STAR-D on treatment resistant depression, TADS for child and adolescent depression) are now coming to an end. Each of these studies involved development of multi-site clinical trial networks that served a large number of subjects in real world treatment settings. What efforts are underway at NIMH to ensure that the important clinical research infrastructure that has been developed continues to help answer important questions about new treatments for mental illness?

Answer. The National Institute of Mental Health (NIMH) is providing infrastructure support to maintain three large networks of investigative clinical teams that have evolved from the practical clinical trials on major depressive disorder (Sequenced Treatment Alternatives to Relieve Depression—STAR*D); schizophrenia (Clinical Antipsychotic Trials of Intervention Effectiveness—CATIE); and bipolar disorder (Systematic Treatment Enhancement Program for Bipolar Disorder—STEP-BD). At the same time, NIMH has been funding a child and adolescent clinical practice network. The networks comprise over 60 sites throughout the United States with continual outreach and engagement to diverse groups of patients and families with mental illnesses. Therefore, the networks are ideally suited for addressing the kinds of real-world "effectiveness" questions that require large and diverse samples and aim to have an impact on clinical practice.

The overarching principle guiding the networks is to conduct research designed to improve the mental health of the public and help better inform clinicians. To accomplish this, research must be informed by broad scientific and public input. In December 2006, NIMH issued a Request for Information (RFI) to solicit suggestions for the most important research directions and projects for the networks. The RFI sought input from investigators, stakeholders, and individuals living with mental illnesses, as well as additional expert advice and guidance from the National Advisory Mental Health Council. Advice was also sought from the NIMH Alliance for Research Progress—a group of patient and family advocates representing national voluntary organizations devoted to public mental health. Feedback from these efforts is being used to develop a list of key research questions and topics. The Institute is currently reviewing this input and will give high priority to those that have the

greatest potential for using resources of the networks to improve the effective use of existing treatments and further development of new interventions.

BIPOLAR DISORDER RESEARCH

Question. Dr. Insel, several years ago, Congress requested NIMH to undertake a national research plan on bipolar disorder. This request resulted in the current research plan on mood disorders at NIMH. Please update the subcommittee on the mood disorders research plan and what NIMH is learning about the causes and new treatments for bipolar disorder.

Answer. NIMH continues to make strides in elucidating the causes of and determining new treatments for mood disorders, including bipolar disorder (BD). Much of this work is guided by goals laid out in "Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research." In addition, yearly progress in research on depression is reported through the Government Performance and Results Act as one of the stated goals for GPRA is to demonstrate through research, reductions in the burdens associated with depression. As one example, in fiscal year 2006 NIMH and its NIH collaborators were able to report significant progress as a result of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study of nearly 2000 depressed patients treated at 41 sites across the nation, including several primary care sites. This landmark study showed that up to 70 percent of those with persistent depression can be successfully treated, yet may need to try several different treatment strategies. By analyzing specific individual patient characteristics, including genes, NIMH funded scientists are now discovering the keys to personalizing and optimizing treatments for depression.

As outlined in the mood disorders strategic plan, NIMH undertakes numerous approaches toward the determination of the underlying causes of BD. While BD has long been known to be heritable, scientists have been unable to identify the key genes involved. Recently, BD has been the focus of a large international effort using whole genome association, a powerful, new approach that permits a screen for variations across the entire genome. Results from 7,000 BP patients and controls should be available later this year, providing the first large-scale, comprehensive scan of genes which contribute risk for BD. Even with these genes, we know that bipolar disorder is not easily diagnosed, especially in children. A recent NIMH-supported study found that BD could be distinguished from another similar childhood syndrome, severe mood dysregulation, through the measurement of the brain's electrical signals. This finding could significantly inform future efforts in diagnosing BD as early as possible.

In terms of improving treatment, in 1998, NIMH undertook a large, national research program to determine best treatment practices for BD. Concluded in 2005, the Systematic Treatment Enhancement Program for Bipolar Disorder continues to inform the field. Recent publications addressed predictors of recurrence for those that had achieved recovery and the effectiveness of different medications in treating those patients who had not shown improvement despite several treatment attempts. According to another recent report, for depressed people with bipolar disorder who are taking a mood stabilizer, adding an antidepressant medication is no more effective than a placebo. These results indicate that careful management of mood stabilizer medications is a reasonable alternative to adding an antidepressant medication for treating bipolar depression. In addition, patients taking medications to treat bipolar disorder are more likely to get well faster and stay well if they receive intensive psychotherapy.

OBSESSIVE-COMPULSIVE DISORDER

Question. Dr. Insel, what recent advances have been made in the area of obsessive-compulsive disorder?

Answer. Obsessive-Compulsive Disorder is an anxiety disorder that is characterized by recurrent, unwanted thoughts (obsessions) and/or repetitive behaviors (compulsions). NIMH has funded several areas of research to understand the causes of and potential treatments for OCD. By studying families with members affected by OCD, NIMH-funded scientists have discovered regions of several chromosomes that may contain OCD susceptibility genes. Previous studies have suggested that the brain chemical serotonin may mediate the compulsive behaviors associated with OCD. Recent work has shown that mice with deletion of certain serotonin receptor genes exhibit impulsive and compulsive behaviors (e.g. burying marbles), suggesting that these mice could be used as models of OCD, and further studies of the serotonin system may provide clues to the etiology of OCD.

Using magnetic resonance imaging, NIMH-funded researchers found that the pituitary glands of children with OCD were smaller than those of healthy children.

The investigators speculate that the smaller volume in patients with OCD might be an effect of abnormal regulation of endocrine function. Further studies might lead to methods for early detection of the disorder.

OCD in adults is known to be a disorder of many different symptoms, but studies have shown that certain symptoms tend to cluster together. Recent NIMH-funded research has revealed several types of symptom clusters—or symptom dimensions—in children and adolescents (e.g. hoarding obsessions and compulsions; symmetry, ordering, and repeating). These symptom dimensions closely mirror those reported in adults with OCD, suggesting relative stability across the course of development. Understanding how these symptoms cluster may help researchers identify the underlying causes of OCD.

Other NIMH-funded studies have suggested a possible link between psychosocial stress and exacerbation of OCD symptoms. In a recent study of children who had OCD, Tourette syndrome (TS), or both OCD and TS, psychosocial stress significantly predicted whether OCD symptoms would worsen in the future. The results suggest that monitoring parental reports of stress, and intervening as appropriate, may help to prevent symptom exacerbations.

Several NIMH-funded studies have focused on treatments for OCD. A recently completed study led to the development of a manual for psychosocial treatment of young children with OCD, with encouraging results on the efficacy of its use. A newly funded study is testing a treatment approach that incorporates self-administered, exposure-based behavior therapy as a low-cost option before implementing therapist-administered exposure. Another study has yielded encouraging pilot results on the efficacy of deep brain stimulation for severe treatment-refractory OCD. Finally, NIMH intramural researchers have evaluated azithromycin and penicillin as a prophylactic treatment for a subtype of OCD; both treatments appeared to reduce exacerbations of OCD symptoms.

STROKE

Question. Dr. Landis, the NINDS made a great advance against stroke with the advent of tPA, the clot-busting drug that can reduce devastating disabilities if given within three hours of the onset of stroke symptoms. Please highlight any recent advances that will help alleviate the burden of this disease.

Answer. Researchers funded by the National Institute of Neurological Disorders and Stroke (NINDS) are making considerable headway into alleviating the burden of stroke, both in preventing new strokes and in treating strokes acutely and chronically. With respect to stroke prevention, NINDS-funded researchers have recently demonstrated that individuals at risk for stroke may benefit from taking multiple preventative therapies, including antiplatelet inhibitors like aspirin, angiotensin-converting enzyme (ACE) inhibitors, and/or statins. These agents exhibit a variety of effects that may lower the risk for future strokes, including reducing cellular stress and inflammation and improving blood flow in the brain. To test the impact of these therapies in combination, investigators conducted a retrospective study of more than 200 patients who presented within 24 hours of stroke onset. Results indicated that individuals taking all three drugs exhibited less severe strokes than did people on a two-drug combination, antiplatelet inhibitors alone, or no stroke prevention therapy. Imaging data also suggested that patients on triple therapy had less at-risk tissue surrounding the damaged regions of their brains and that triple therapy appeared to be linked to shorter hospital stays and better function at hospital discharge. Although these data are preliminary, they provide support for the further exploration of the impact of this combination regimen on the prevention of severe strokes.

With respect to acute stroke treatment, many potential new therapies are in the pipeline. Research teams in the NINDS-funded Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS) are exploring many different options to treat acute stroke, including a combination of ethanol, caffeine and hypothermia for neuroprotection; the efficacy of using a clot-removal device to improve post-stroke outcomes; adding extra drugs to the clot-buster tissue plasminogen activator (tPA) that may increase the potency of tPA in disrupting a clot, so that less tPA is needed; and the delivery of the potential neuroprotectant magnesium sulfate by emergency responders, to try to prevent cell loss by intervening as early as possible for acute ischemic stroke.

Rehabilitation following stroke has also entered a new era, since National Institute of Child Health and Human Development (NICHD) and NINDS-funded research demonstrated in 2006 that constraint-induced movement therapy—a rehabilitative technique that involves forced use of a partially paralyzed arm—could promote a 34 percent faster recovery in the affected arm than could standard therapy

if applied 3–9 months after stroke, and could contribute to an increased ability to perform tasks of daily living with the impaired arm and hand. These results provide evidence of significant intervention efficacy from one of the first major large-scale randomized trials of stroke rehabilitation and investigators are now hoping to test this therapy in a phase III trial at even earlier time points after stroke.

PARKINSON'S DISEASE

Question. Dr. Landis, despite the constraints presented by a flat proposed budget, there are agreed-upon, high-priority research areas for Parkinson's disease. Please describe what the NINDS is doing to ensure that those high-priority areas are getting treated as high priorities and are being funded, and in a timely manner. Do you have a strategic plan for Parkinson's disease research that includes a budget? Are you following it? Does it include funding for those high-priority research areas?

Answer. The National Institute of Neurological Disorders and Stroke (NINDS) leads the implementation of PD research efforts at the National Institutes of Health (NIH), in large part by following the priorities outlined in its 2006 PD Research Plan (http://www.ninds.nih.gov/funding/research/parkinsonsweb/PD_Plan_2006.htm). The Institute considers these needs, along with those in many other disease areas, each time it assesses potential grant solicitations and other programs for future implementation. While NINDS does take priorities from its PD planning efforts very seriously, it does not develop specific budgets for any of its disease plans prior to their implementation, since appropriations and other emergent public health needs and opportunities are not known in advance. In the past, the absence of specific budgets for disease priorities has not hindered progress. In the first five years of the implementation of the PD Research Agenda, NIH and NINDS-funded researchers made tremendous progress on several fronts, including advances in understanding the genes involved in inherited PD and the unexpected contributions made by screening large numbers of genes for clues regarding the role that genetic variability may play in sporadic PD. Researchers also made substantial progress in understanding how PD occurs at a cellular level and how treatments like gene therapy may be able to protect against further brain deterioration. NINDS is poised to continue this progress, and the Institute has already provided funding to address a number of priorities identified in the 2006 PD Research Plan. Examples of two of these programs are provided below.

First, the 2006 PD Plan highlighted further exploration of the non-motor aspects of PD—which can include sleep abnormalities, fatigue, behavioral and cognitive impairments, anxiety, and depression—as a major research priority. As just one example of possible implementation of this priority, the external scientists and members of the PD patient community who developed the Plan's recommendations strongly suggested that non-motor manifestations of PD be assessed in more clinical trials. The NIH Exploratory Trials in Parkinson's Disease (NET-PD) phase III trial—a large, randomized clinical trial of the potential neuroprotective agent creatine—will address this need directly, by exploring the ability of creatine to improve some of the non-motor features of PD in addition to its ability to slow the progression of the motor symptoms.

Second, the 2006 PD plan also identifies PD biomarkers, which enable clinicians and researchers to track disease risk, activity, progression and response to treatment, as a very high priority for the field. In October 2006, the NINDS and the other NIH Institutes and Centers participating in the NIH Blueprint for Neuroscience Research program addressed this recommendation by issuing a grant solicitation to encourage research on biomarkers for neurodegenerative diseases, including PD. This solicitation elicited a vigorous response from the research community and the grant applications are currently under review.

OUTREACH ON ADDICTION RESEARCH

Question. Dr. Volkow and Dr. Li, what are your institutes doing to infuse your research on addiction into local treatment centers—where the rubber meets the road? How does NIDA and NIAAA work with States, and the directors of State substance abuse systems, to ensure that the research done by NIDA and NIAAA reaches into our local clinics and treatment systems to make a difference?

Answer. NIAAA is engaged in considerable outreach to increase use of research-proven treatments in community treatment centers. First, NIAAA has produced a variety of research summaries and practical tools to assist in dissemination and implementation of research findings. The 2005 Edition of the NIAAA Clinicians Guide (updated in 2007) has been very popular for health care professionals. NIAAA staff are currently working on training programs for health care professionals centered around the Guide, a version of the Guide for non-prescribing professionals, and a

Self-change Guide (called “Rethinking Drinking”) aimed at consumers and concerned others. Second, NIAAA staff work closely with SAMHSA staff, providing research summaries, advice, participation in various work groups, and written and computerized tools to assist SAMHSA staff in their interactions with States systems and directors. Third, NIAAA works with other federal agencies such as VA, AHRQ, DOD, CDC and CMS to facilitate implementation of new research on treatment.

NIDA is taking a collaborative approach aimed at proactively involving all entities invested in changing the system and making it work better—so that research results do not linger the customary 15–20 years before they are implemented as part of routine patient care. One way this occurs is through the testing of drug abuse treatment approaches directly in the community settings where they will be used with real-world populations by counselors trained to implement them. This is the work of NIDA’s National Drug Abuse Treatment Clinical Trials Network (CTN), which not only involves practitioners from community treatment programs (CTPs) in formulating research protocols, but also in providing real-world feedback on their success and feasibility.

NIDA is taking a similar approach to enhance treatment for drug-addicted individuals involved with the criminal justice system through our CJ-DATS (Criminal Justice-Drug Abuse Treatment Studies) initiative. Research supported through CJ-DATS is designed to effect change by bringing new treatment models into the criminal justice system and thereby improve outcomes for offenders with substance use disorders. It seeks to achieve better integration of drug abuse treatment with other public health and public safety forums, and represents a collaboration of NIDA, the Substance Abuse and Mental Health Services Administration (SAMHSA), the Centers for Disease Control and Prevention, Department of Justice agencies, and a host of drug treatment, criminal justice, and health and social service professionals.

In addition to testing and evaluating protocols in the settings in which they will be used, NIDA works with our colleagues to create change at multiple levels and bridge the divide between scientific findings and their implementation. Our Blending Initiative exemplifies this approach and involves regular stakeholder conferences, a partnership with SAMHSA to support the work of Addiction Technology Transfer Centers (ATTCs) in training and disseminating research-based practices to community practitioners, and our ongoing relationship with State representatives and substance abuse directors. The Blending Initiative is helping to catalyze change by “seeding” the field with research-based practices and innovative products to facilitate their use. Specifically, Blending Teams made up of practitioners and researchers develop training modules and other dissemination products based on NIDA research, and thereby help implement and sustain effective drug abuse treatments in myriad settings.

On way in which NIDA continues to build and enhance our productive partnership with state directors of substance abuse agencies is through annual meetings with their national association—the National Association of State Alcohol and Drug Abuse Directors (NASADAD)—to identify strategies for accelerating the adoption of evidence-based practices into State drug abuse prevention and treatment programs. We are gratified that State directors now consistently look to NIDA for credible information about selecting, implementing, and sustaining science-based and cost-effective treatment and prevention interventions.

For example, NASADAD has embraced the promise of buprenorphine as an opioid abuse treatment option, developing a State Issue Brief on the topic and probing States for their specific needs. In response, States have identified technical assistance needs and areas where their Addiction Technology Transfer Centers (ATTCs) could provide support (e.g., training, best practice guidelines, dissemination packets, and strategies to further partnerships with physicians). Their feedback suggests new and expanded roles for existing treatment program medical directors of State Alcohol and Drug Abuse agencies. Moreover, most States have already begun aggressive outreach programs to approved physicians to provide them with expanded training and educational opportunities, both directly and in partnership with other entities.

NIDA views the translational process as comprising systems-level factors aimed at continuous improvement. In that vein, a collaborative initiative—the NIDA-SAMHSA RFA, “Enhancing State Capacity to Foster Adoption of Science-Based Practices”—encourages state agencies to team with research organizations to optimize their research infrastructure for evaluating delivery of publicly supported drug abuse treatment or prevention services. Several grants received initial funding in fiscal year 2006 to facilitate adoption of meritorious science-based policies and practices, including developing ways to measure and track program fidelity, promote adoption of research-based practices in addiction treatment, and streamline data collection and reporting requirements.

Enhancing the adoption of research-based practices by state-based systems is a strong NIDA commitment and will continue to be a top priority since it ensures that new scientific discoveries are translated into prevention and treatment interventions that are adopted by the community.

ADDICTION AND OBESITY

Question. Dr. Volkow, how are findings from your research linked to obesity?

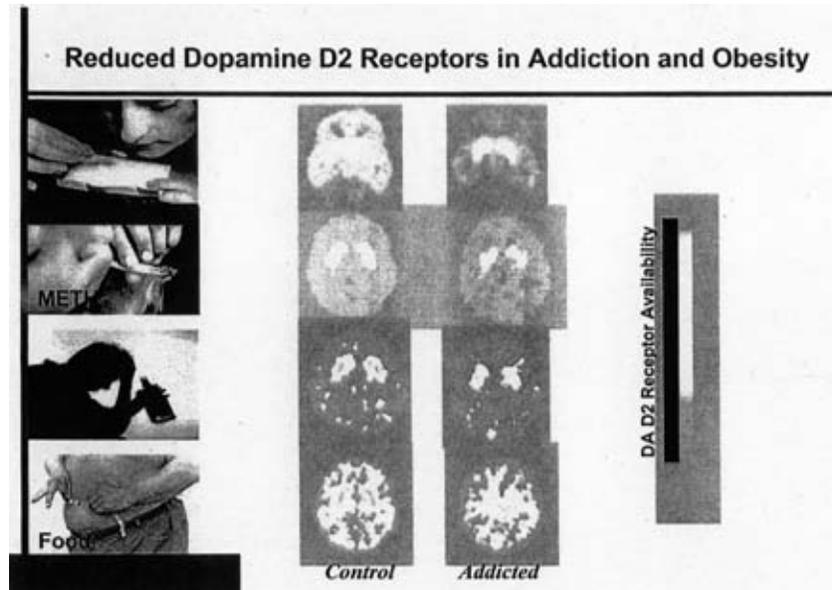
Answer. Animal studies and brain imaging studies in humans reveal similarities in the way circuits and neurotransmitter systems act in the rewarding effects of both food and drugs of abuse (e.g., opioids and other peptides, dopamine, cannabinoids). When imaged, the brains of both obese and drug-addicted people show a surge in dopamine when presented with food- or drug-related stimuli, respectively, and both show similar reductions in availability of dopamine receptors, suggestive of a less responsive reward system. Further, both obesity and drug addiction can be characterized by excessive, repetitive behaviors often marked by the inability to change or stop in the face of severe negative health consequences.

Given these parallels, few fields offer as much potential for cross-fertilization as addiction and obesity research. In the treatment arena, it is noteworthy that some of the behavioral interventions beneficial for treating drug addiction (e.g., incentive motivation, cognitive—behavioral therapy) may also be helpful in treating obesity, and several potential candidates for the pharmacological control of food intake (e.g., the cannabinoid receptor antagonist Rimonabant and the appetitive molecule orexin) also show promise for drug addiction.

UNDERAGE DRINKING

Question. Dr. Li, on March 6, the U.S. Surgeon General issued a “Call to Action on Underage Drinking”, which underscored that alcohol “remains the most heavily abused substance by America’s youth.” It also calls for changing public attitudes toward youth alcohol use. That includes making it harder for young people to have access to alcohol. Are you doing any research on the most effective ways to reduce the availability of alcohol to underage youth?

Answer. NIAAA’s comprehensive research portfolio on reducing underage drinking addresses both the demand for alcohol by youth as well as their access to it. Both components include approaches that target individuals, families, schools, communities and the overall environment. To reduce the appeal of alcohol to youth, NIAAA supports research on positive youth development including the ability to resist alcohol and other drugs. To address the supply of alcohol to youth, NIAAA supports a number of studies on the most effective ways to reduce the availability of alcohol to underage youth from late childhood through age 21. For example, some studies are testing the effectiveness of campus-community coalitions in reducing underage alcohol use by students in America’s colleges and universities. These include promising studies comparing campuses that adopt comprehensive community interventions with control campuses that are doing business as usual. Other research studies are addressing neighborhood and community level interventions. For example, a recent study showed that an intervention for 15–29 year olds incorporating community mobilization, community awareness, responsible beverage service, underage alcohol access law enforcement and intoxicated patron-law enforcement was effective in reducing sales to minors as well as adverse outcomes related to alcohol in the targeted age group. At the community and state level NIAAA is funding studies evaluating the effects of policy changes on underage drinking. In addition, NIAAA is evaluating two separate community based OJJDP initiatives both of which include components aimed at reducing the availability of alcohol to youth. One is focused on rural communities in seven states and the other is focused on four Air Force bases and their surrounding communities.



Question. We all know that young people are exposed to a wide range of messages in the media about alcohol—both positive and negative. Are you doing any research on how their exposure to these messages affects whether they will become dependent on alcohol?

Answer. Given that early initiation of alcohol use, and especially early binge drinking, is associated with an increased risk of future alcohol dependence, it is important to identify factors that influence a young person's decisions about drinking. With respect to media influences, NIAAA funds research addressing the relationship between underage drinking and exposure to messages about alcohol, including advertising. However, assessing the effect of advertisements on the drinking behavior of individuals or populations is complicated. It is often difficult to ascertain the specific effects of advertising since they must be measured against a background dense in alcohol messages and images. Nevertheless some interesting findings have emerged. For example, in a widely-cited recent study, investigators interviewed a sample of youth aged 15 to 26, from 24 Nielsen media markets, on four occasions over a period of 21 months about their drinking. Advertising exposure in the study was measured both subjectively in terms of reported exposure and objectively in terms of advertising expenditures. It was concluded that each additional advertisement seen increased the number of drinks consumed in the past month by 1 percent. Further, youth in markets with greater advertising expenditures drank more: for each additional dollar spent per capita, the number of drinks consumed per month increased by 3 percent. More longitudinal studies such as this are needed.

In addition, who sees/hears alcohol advertising and who is affected by it is an important issue. While almost all persons are exposed to significant amounts of alcohol advertising, youth may be at risk for overexposure. Others such as dependent drinkers, or those in recovery, for whom alcohol ads may provide drinking cues or triggers, may be especially vulnerable to advertising. A recent study comparing teens with and without alcohol use disorders (AUD) found that teens with AUD showed substantially more brain activation to pictures of alcoholic beverages than controls (Tapert et al. 2003).

Additional research on adolescent decision-making will provide greater understanding of the factors that influence underage drinking behavior including initiation and escalation of alcohol use and binge drinking. This includes but is not limited to studies on media influence.

Question. This question is about treatment, and why some people improve their behavior. I was interested to read in your testimony that there's a debate whether the treatment itself is responsible, or whether it results from the positive motivation in seeking treatment. You also write that a wide array of approaches yield similar

results, suggesting that it's not the particular technique that's responsible for change but other common underlying factors. Tell me more about this—are most forms of treatment being used today generally equally effective? Is the most important thing simply getting the person into treatment?

Answer. Research has established that several forms of behavioral treatment (cognitive-behavioral treatment (CBT), motivational enhancement therapy (MET), and twelve-step facilitation (TSF), yield roughly equivalent outcomes. In the year following treatment with one of these therapies, drinking is reduced by about 85 percent compared to the period immediately prior to treatment. Overall, about one-third of alcohol dependent persons undergoing treatment will either be abstinent or not engaging in any high-risk drinking, about one-fourth will not respond to that episode of treatment (although they may respond to future treatment), and the remainder have markedly reduced drinking and alcohol-related consequences, but are not entirely well. Over time, many of this latter group eventually become abstinent. Naltrexone, a medication for reducing relapse, yields similar results when combined with brief counseling by a doctor or nurse. Since there is no single type of treatment that is generally more effective than others, “simply getting the person into treatment” does seem to be more important than which treatment they engage in. However, on a practical level, people have clear preferences about what kind of treatment they would like, so offering a menu of currently supported approaches is likely to maximize the likelihood that one of them will be appealing enough to engage the affected individual.

How well treatment provided in the community compares with the treatments used in the studies undoubtedly varies. Although a precise estimate of the effect of this deviation is not available, there is evidence that some practices that are not helpful still persist in some community programs. Additionally, most treatment programs fail to make patients aware of various treatment options available, including medications. One study found that 93 percent of programs offer only twelve-step oriented behavioral treatment. Although this type of program may be as effective as others, it means that most people do not have a meaningful choice if they wish to receive treatment.

Although treatment appears to improve outcomes, the most significant are those commonly seen among all treatment-seekers. Common examples include a driving while intoxicated charge, an employer referral, or an ultimatum from a spouse. This process is the focus of an innovative new research program called the Mechanisms of Behavior Change Research Initiative.

QUESTIONS SUBMITTED BY SENATOR DANIEL K. INOUE

SUICIDE

Question. Dr. Insel, suicide is a major, preventable public health problem. In 2004, suicide was the 11th leading cause of death in the United States, accounting for 32,439 deaths. In Hawaii, for young people age 15–34 years, suicide is the second leading cause of death—second only to accidents. What type of research is NIH conducting with respect to the causes of and the best practices for the prevention of suicide?

Answer. NIMH has a long-standing commitment to supporting research on suicide risk and prevention. In response to the 2002 Institute of Medicine Report, “Reducing Suicide: A National Imperative,” NIMH, NIDA, and NIAAA issued a request for applications and funded three centers focused on intervention and prevention of suicide. Now in their third year of support, the centers have conducted pilot intervention studies with patients suffering from mental and substance use disorders.

These centers have also engaged in a number of collaborative efforts. Federal staff (NIH, CDC, VA, SAMHSA, IHS) and investigators from the centers have interacted via workgroups focused on methodological challenges in suicide research, such as developing common measures of suicidality as well as understanding the role of impulsivity in suicide risk. The American Foundation for Suicide Prevention funded a pilot project with the centers to create a registry of suicide attempters. This registry will facilitate understanding of the quality of care across services settings, as well as the longer-term outcomes of acute treatment of adolescent suicide attempters. One of these centers also played a key role in re-reviewing suicidal events for the FDA’s 2005 review of potential suicidal side effects of antidepressants. As a follow-up to the FDA review, in 2006, NIMH funded five research projects to examine the association between antidepressant medications, notably selective serotonin reuptake inhibitors (SSRIs), and suicidal thoughts and actions. These projects will help determine why and how SSRIs may trigger suicidal

thinking and behavior in some people but not others, potentially leading to new tools that can be used to screen individuals who are most vulnerable.

Suicide patterns in the United States vary significantly in terms of demographics and cultures. For example, older white males have the highest suicide rate; are likely to have had a late onset of major depression; and are likely to have been seen in a primary care setting within the month of their death, without being diagnosed or treated for depression. To address this issue, NIMH funded a study called the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) to test approaches to improve identification and treatment of older adults with depression in primary care settings. Results from PROSPECT indicated that a collaborative care approach to treating depression in primary care more effectively reduced suicide ideation as well as depressive symptoms, compared to treatment as usual.

American Indian, Native Alaskans, Native Hawaiians, and other indigenous peoples in the United States. Territories have the highest suicide rates among youth. To address the problem, NIMH, in collaboration with other NIH offices and Institutes, worked with the Indian Health Service, Health Canada, and the Canadian Institutes of Health to convene a bi-national conference in 2006 entitled "Indigenous Suicide Prevention Research and Programs in Canada and the United States: Setting a Collaborative Agenda." Community members and research partners discussed the importance of cultural knowledge in developing interventions and considered best practices that could be shared in developing partnerships and infrastructure.

NIMH-supported research has demonstrated that several promising treatments significantly reduce the risk for suicide re-attempts; these treatments include cognitive behavioral interventions provided to individuals who have made a recent suicide attempt, as identified through emergency room departments, as well as dialectical behavior therapy provided to individuals with borderline personality disorder. NIMH is also using knowledge gained from previous research studies to guide the conduct of clinical trials involving individuals at high risk for suicide. The Institute recently completed a series of practical clinical trials focused on treatments for schizophrenia, depression, and bipolar disorder. The individuals enrolled in these trials were closely monitored for suicidal behavior and were provided appropriate crisis treatment when necessary.

ALZHEIMER'S

Question. Dr. Insel, less than two weeks ago a new report was released indicating that there are now 5 million Americans with Alzheimer's disease and that this number is projected to increase by 50 percent to 7.7 million by 2030. Given that advancing age is the greatest risk factor for Alzheimer's disease and that the number of Americans surviving into their 80's and 90's is expected to grow, what specific studies are underway at NIMH to address the challenges posed by Alzheimer's disease?

Answer. NIMH supports research on a broad range of topics pertaining to older adults with Alzheimer's disease, ranging from basic research on the disorder to clinical interventions and services research that may assist affected individuals with their symptoms and problems in day-to-day living. A primary concern in NIMH research is to improve our understanding of, and techniques for managing, the psychiatric disorders and behavioral disturbances that often accompany Alzheimer's disease and related dementias.

Recently published results from NIMH's large scale Clinical Antipsychotic Trials for Intervention Effectiveness in Alzheimer's Disease (CATIE-AD) study highlight the challenge of managing agitation and behavioral problems in Alzheimer patients. Although some patients with these problems may benefit from treatment with atypical antipsychotic medications, the evidence from this study suggests that these medications hold limited value for the majority of patients and that the benefits are often offset by intolerability of medication side effects. These results indicate the need for research on alternative treatment approaches, including nonpharmacological interventions. Additional analyses of the data from the CATIE-AD trial are ongoing.

Earlier work supported by NIMH established criteria for assessing a specific syndrome of depression that is commonly manifested in Alzheimer's disease and making this a target for treatment. The Institute is now in the fifth year of supporting a multi-site clinical trial studying pharmacologic treatment of Depression in Alzheimer's Disease (DIADS-2) and its impact on functional capacities in Alzheimer patients.

NIMH supports various basic and intervention studies designed to improve clinical management of other psychiatric and behavioral disturbances associated with Alzheimer's disease, such as the common pattern of sleep disturbance and nocturnal agitation. For example, one current NIMH study investigates sleep disorder in peo-

ple who have mild cognitive impairment, a precursor to Alzheimer's disease, and an intervention trial is evaluating alternative treatments for insomnia among older patients with dementia.

Numerous NIMH studies examine potential risk factors for developing Alzheimer's disease in the hope that understanding these factors may inform efforts to develop preventive interventions. Research areas include genetics, brain structure, cognitive performance, and various other risk factors in young and middle-aged adults to determine whether it is possible to identify elements of risk prior to the appearance of clinical manifestations of illness. One study has been examining the deleterious effects that depression may have over time, potentially leading to central nervous system damage, cognitive decline, and the development of states of Mild Cognitive Impairment and dementia.

NIMH also supports basic neuroscience research on etiological and athophysiological actors in Alzheimer's disease, including numerous studies investigating key cognitive processes and how these are related to normal and abnormal brain functioning.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

FABRY DISEASE

Question. There are a number of individuals currently participating in efforts conducted by the Developmental and Metabolic Neurology Branch at NINDS. There is concern that when the Branch closes, as it will due to the retiring of Principal Investigator (PI) Roscoe Brady, the efforts that are benefiting the lives of so many, in particular those that are living with Fabry Disease, Gaucher Disease, Tay-Sachs and others, will also cease. Can you explain the rationale behind the NINDS' decision to close the Branch indefinitely and not continue these efforts under the leadership of another PI?

Answer. Following Dr. Brady's retirement, NINDS made the decision to close the Developmental and Metabolic Neurology Branch (DMNB), which is part of NINDS' intramural program (the component of the NINDS that is located on the NIH campus in Bethesda, MD). However, the closing of this branch certainly does not mean that NINDS efforts in lysosomal storage disorders (LSDs), including Fabry and Gaucher disease, will cease. Groundbreaking research on lysosomal storage disorders conducted by this Branch has provided a strong foundation for research in these areas to continue through the NINDS extramural program (research funded by NINDS that is carried out at universities, medical centers, and small businesses throughout the United States). In fact, the extramural program accounts for approximately 90 percent of NINDS' annual budget and NINDS already funds a large portfolio of extramural grants focused on understanding and treating these disorders. In addition to NINDS, a number of other Institutes and Centers at NIH also support research through their extramural programs on lysosomal storage disorders, including Fabry disease. These grants aim to better understand and treat these disorders, with a number of projects focused specifically on developing gene therapy approaches to treatment. Furthermore, based on the successes from forty years of research in the DMNB led by Dr. Roscoe Brady, companies have developed and marketed enzyme replacement therapy for several of these diseases and are conducting additional clinical trials to improve treatment using other therapeutic strategies. In terms of clinical care, there are currently over 100 medical centers across the country with experience in diagnosing, treating, and managing care of patients with lysosomal storage disorders.

NINDS' decision to close the DMNB was reached after much deliberation and after receiving input from the NINDS Board of Scientific Counselors, an external advisory group that reviews and evaluates the NINDS intramural program. NINDS and the Board of Scientific Counselors determined that the research and clinical care efforts that used to be unique to the Branch are now well represented at medical schools, research institutes, and tertiary care centers throughout the country. They recommended that the NINDS intramural program identify other rare neurological disorders that have lagged significantly behind Gaucher and Fabry disease and could benefit as they have from an intramural effort.

Question. Can you provide additional information regarding the efforts of the branch on solving the problems that still exist with enzyme replacement therapy? How will the progress that has been made on these issues continue if the efforts of this Branch are stifled due to its closing?

Answer. The DMNB was instrumental in developing enzyme replacement therapy, which is used to treat a number of the LSDs, including Fabry, Gaucher, and Pompe

disease. While enzyme replacement therapy significantly improves the quality of life for patients with these disorders, the treatment is not sufficient to address all the symptoms, particularly those resulting from deficits in the central nervous system. This is due in part to the incomplete access of the enzyme replacement to the central nervous system (CNS) because of the blood-brain barrier (a semi-permeable barrier that prevents materials in the blood from entering the CNS). NINDS, through its extramural program, funds a number of grants focused on facilitating the access of enzyme replacement to the CNS by protein reengineering, increased dosing regimen, and alternative delivery routes. NINDS also funds extramural research focused on developing other therapeutic approaches including substrate reduction (decreasing the production of the molecule that is accumulating in the disease), and pharmacological chaperones (small drugs that can specifically target and stabilize the defective enzyme, enhancing any residual activity). Longer-term therapeutic strategies such as stem cell transplantation and gene therapy are also being funded by NINDS.

One of the goals of the NINDS intramural program is that research conducted there lay the groundwork for a broader based research effort in the extramural community. Historically, closure of other NINDS programs has proven the intramural program's success and shown that the research initiated by these branches can be effectively graduated into the extramural research community. For example, research carried out in a branch that focused on therapeutics for Parkinson's disease set the stage for a rigorous therapeutics development program on Parkinson's disease through the NINDS extramural program. Similarly, work carried out by an NINDS lab that demonstrated the transmissibility of Creutzfeldt-Jakob disease (CJD) helped stimulate research in the extramural community to better understand this and other disorders in the class of transmissible spongiform encephalopathies. It is our expectation that ongoing and future research through NINDS's extramural program will continue to improve the lives of individuals with LSDs.

Question. What other work are you planning to do to improve both the quality and quantity of life of those living with Fabry disease?

Answer. As I have just described, NINDS, through its extramural research program, funds research projects focused on developing new and more effective treatment strategies to improve the quality and quantity of life for those individuals with Fabry and other disorders. A number of these grants have been submitted through an ongoing NINDS Program Announcement with Set-aside funds (PAS), entitled "CNS Therapy Development for Lysosomal Storage Disorders." This funding opportunity announcement was started in 2004 and since then many new promising therapeutic approaches are being investigated.

Partnering with patient voluntary groups is another way that NINDS hopes to advance research and improve the lives of patients with these disorders. The PAS mentioned above is co-sponsored by the Lysosomal Storage Disease Research Consortium (LSDRC), a collaborative research-funding group comprising LSD patient support groups and private family research foundations. In addition, the NINDS organizes a number of workshops in order to identify scientific gaps and opportunities related to various LSDs, and to foster collaboration between the researchers. Several of these workshops have been organized in conjunction with some of the patient voluntary groups. To promote the exchange of ideas on research across the many LSDs, the NINDS helped form the Lysosomal Disease Network. This consortium of scientists, healthcare professionals and clinics work to improve basic knowledge and understanding of LSDs, improve diagnosis, and advance therapeutic options for individuals affected by these disorders. The NINDS has supported the first two annual meetings of the Lysosomal Disease Network.

EPILEPSY

Question. I understand that last week, NINDS hosted the second Conference on the Cure for Epilepsy. What new information did this conference yield about epilepsy and are we any closer to finding a cure?

Answer. In March 2007, the NINDS co-sponsored a large conference, entitled: "Curing Epilepsy 2007: Translating Discoveries into Therapies." The Conference was well-attended by the basic and clinical research communities, and specific sessions at the Conference focused on research conducted by junior investigators; the translation of advances in the genetics of epilepsy and our understanding of how epilepsy arises (epileptogenic mechanisms) into therapies; cognitive and psychological issues in epilepsy; and emerging technologies in diagnostics and cellular and molecular therapeutics. The meeting also involved presentations from several patients and patient representatives on their personal experiences with epilepsy.

Several very exciting trends in epilepsy research were emphasized at the meeting. First, the ideal way to treat (and cure) epilepsy would be to prevent the development of seizures in the brain, not just to stop them from progressing or diminish their behavioral effects (e.g., seizures). A growing appreciation in the scientific community as to why neuronal circuits in the brain develop abnormal patterns of overexcitation is now enabling investigators to identify tangible therapeutic targets that may interfere with the earliest molecular events in the development of seizures. This shift heralds the availability of substantially more effective therapies for epilepsy. Second, advances in imaging are also making a dramatic impact on a number of disciplines in epilepsy research, including the development of biomarkers of seizure-prone brain regions, the characterization of the effects of epilepsy on brain development, and the cognitive impact of the disorder. The use of these techniques will facilitate epilepsy diagnostics as well as treatment. Third, completely new therapeutic approaches are emerging in epilepsy research, including the possibility that cell-based therapies may be able to restore normal patterns of activity in seizure-prone brain circuits and advancements in nanotechnology may improve devices that sense impending seizures with greater accuracy than ever before.

Question. Are we putting adequate resources toward epilepsy research at NINDS to find a cure for epilepsy? In addition, I understand that new cases of epilepsy are most prominent in seniors (those aged 65 and older). What are we doing to better understand the cause of seniors having seizures and will NIH partner with other entities to study this emerging area?

Answer. The National Institute of Neurological Disorders and Stroke (NINDS) has invested considerable funding to identify and test potential therapies for epilepsy. Currently, the NINDS is funding nine clinical trials in epilepsy, including phase III trials of drug therapy for childhood absence epilepsy and the use of progesterone therapy to reduce intractable seizures in women whose seizure severity is linked to their menstrual cycle. In addition to these and other ongoing trials, the NINDS also continues to support its Anticonvulsant Screening Program (ASP), a public-private partnership program designed to evaluate the potential efficacy and toxicity of pre-clinical candidate compounds in validated epilepsy model systems. In 2006, the ASP screened several hundred molecules for potential activity against epilepsy and related disorders. The Program has participated in the evaluation and development of eight currently marketed antiepileptic drugs, and nine new ASP compounds are currently in clinical testing.

In addition to these efforts, the NINDS has also funded a number of epilepsy grants as part of its broad translational research program, which is designed to accelerate therapeutics research towards early clinical testing. Topics of these awards range from a study of specific chemical pores on neurons and their role in neonatal seizures to the preclinical development of the anticonvulsant chlorokynurenic acid—which effectively accesses the brain when administered systemically—as a therapeutic agent for both adults and children with epilepsy.

With respect to the study of epilepsy and the elderly, the NINDS has provided funding to several grants including a large multi-investigator award focused on patterns of use of antiepileptic drugs in the elderly and the differences in breakdown of antiepileptic medications in older versus younger individuals. Understanding these patterns and differences is critical to their proper treatment (including dosing and avoidance of toxicity). In addition, stroke is a primary cause of epilepsy in the elderly, and NINDS-funded basic science researchers are developing a model of this form of epilepsy for subsequent use in understanding how seizures develop after stroke and how therapies might prevent and/or treat these events. The NINDS also meets regularly with a number of other National Institutes of Health (NIH) Institutes as part of the NIH Interagency Epilepsy Coordinating Committee meeting and would welcome potential collaborations in the area of aging and epilepsy as they emerge.

Question. In 2002 NINDS conducted research on TBI and epilepsy. Given the increased number of cases of TBI due to the war in Iraq, will NINDS be studying the relationship between TBI and epilepsy for updated statistics and data?

Answer. The primary role of the National Institute of Neurological Disorders and Stroke (NINDS) with respect to all types of epilepsy research—including that induced by traumatic brain injury (TBI)—is to provide support for research on the prevention, diagnosis, underlying causes, and treatment of this condition. The NINDS is currently supporting several studies that may reveal links between TBI and epilepsy, including an exploration of early post-injury changes in brain activity and its impact on affected neurons; the effects of structural changes in neuronal circuitry on the development of posttraumatic epilepsy—particularly in those circuits that help to prevent overexcitability in the brain—and the impact of head injuries on abnormal sprouting of undamaged neurons and the tendency of these new nerve

pathways to become overly active. In addition to these basic studies, the NINDS is also funding a pilot clinical trial to test whether very early administration of the anticonvulsant drug levetiracetam can prevent posttraumatic epilepsy in adults as well as children. In this early-phase trial, researchers will explore the safety and tolerability of the drug in individuals with TBI and the feasibility of initiating treatment within eight hours of injury. If the pilot data are promising, the research team will utilize the results to build a larger-phase clinical trial.

The mechanisms that underlie the development of epilepsy were also a focus of the March 2007 Curing Epilepsy Conference; specifically, the meeting included an entire session on the development of epilepsy, including TBI as a major environmental contributor. Discussions in this part of the meeting and during a session on the NINDS Epilepsy Benchmarks—a series of specific scientific goals for the epilepsy research community—confirmed that understanding how epilepsy develops is a very high research priority and should be a focus for the epilepsy community in the coming years.

Although these and other studies funded by the NINDS are likely to inform researchers and ultimately clinicians on the best way to prevent and/or treat posttraumatic epilepsy, it is the Centers for Disease Control and Prevention (CDC) that typically collect statistics and study trends on medical conditions. Because of the increasing number of war injuries that involve TBI and the urgency in addressing the medical needs of these soldiers, the NINDS staff has established a working group with relevant government partners, including the Department of Defense, the Department of Veterans Affairs, the CDC, and others to discuss scientific topics of mutual interest and develop collaborations in these areas. Following the first meeting of the group last September, NINDS set up a listserv for timely dissemination of information on TBI research across these multiple agencies. The NINDS staff is planning another meeting for the summer of 2007.

FUNDING RESEARCH ON SEVERE MENTAL ILLNESS

Question. What is NIMH doing to fund more research on severe mental illness, as called for by national organizations such as the National Alliance for Mental Illness and Mental Health America?

Answer. NIMH supports innovative research that promises to profoundly transform the diagnosis, treatment, and prevention of mental disorders, paving the way for a cure. Mental disorders are the leading cause of disability in the United States and Canada for ages 15–44,¹ and each year, roughly 12 million people report symptoms of mental illness so severe as to cause significant disability and interference with everyday living.² To address these critical health needs, the Institute supports, conducts, and promotes research that spans the continuum from basic research on brain and behavioral processes that provides the foundation for understanding mental disorders, to investigations of improved pathways for the rapid dissemination of evidence-based practices into mental health care and service efforts.

Along this continuum, the Institute is supporting several key areas to ensure that each step along the pathway from scientific discovery to the implementation of improved interventions is fully supported. For example, NIMH is providing infrastructure support to maintain three large networks of investigative clinical teams that have evolved from the recent NIMH practical clinical trials on major depressive disorder, schizophrenia, and bipolar disorder. These practical trials were “effectiveness studies” designed to examine not only changes in symptoms but changes in “real world” functioning. The networks comprise over 60 sites throughout the United States with continual outreach to, and engagement of, diverse groups of patients and families with mental illnesses. The overarching principle guiding the networks is to conduct research designed to improve the mental health of the public and to help better inform clinicians, families, and policy makers—efforts that require participation from the diversity of people and settings involved in health care.

NIMH continues its strong commitment to investment in research to elucidate the causes of and best treatments for schizophrenia. Although current medications are reasonably effective in treating symptoms such as hallucinations and delusions, these treatments provide little relief for the cognitive problems (e.g., memory, attention) responsible for much of the long term disability associated with schizophrenia. To address this issue, NIMH funded the Measurement and Treatment Research to

¹The World Health Organization. The World Health Report 2004: Changing History, Annex Table 3: Burden of disease in DALYs by cause, sex, and mortality stratum in WHO regions, estimates for 2002. Geneva: WHO, 2004.

²Kessler RC, Chiu WT, Demler, O, Merikangas, KR, Walters, EE. Prevalence, Severity, and Comorbidity of 12-Month DSM-IV Disorders in the NCS-R. Arch Gen Psychiatry. 2005 Jun; 62: 617–627.

Improve Cognition in Schizophrenia (MATRICS) program. MATRICS brought together representatives from academia, industry, and government in a consensus process to address obstacles that are likely to interfere with the development of pharmacological agents for treating cognitive deficits associated with schizophrenia. As a result of MATRICS, researchers developed several comprehensive assessment tools to measure cognitive functioning abilities in patients with schizophrenia. To build upon the work from MATRICS, NIMH has also supported a network of Treatment Units for Research on Neurocognition and Schizophrenia (TURNs). The network is about to begin testing the safety and efficacy of new therapeutic compounds for treating the cognitive deficits of schizophrenia.

In fiscal year 2008, through a Requests for Applications, NIMH will invite research grant proposals focused on early detection, prevention, and treatment of schizophrenia. These initiatives will foster research to define critical moments in the disease course, such as a first psychotic episode, and will promote the development of unique early interventions to pre-empt the serious disability caused by schizophrenia.

SERVICES RESEARCH FOR SEVERE MENTAL ILLNESS

Question. How is NIMH working to promote more research on what services lead to recovery for people with severe mental illness, as called for by the President's Mental Health Commission?

Answer. NIMH supports research to establish an evidence-base for interventions and service systems that will provide citizens with the best possible care. Within this context, NIMH funds a program of research on disability and community reintegration, which focuses on ways to reduce the disability of people with mental illness through connective services within their communities. For example, an NIMH-funded study is identifying the most effective strategies for building a partnership between university-based clinical services researchers and practitioners and consumers from a psychosocial rehabilitation service agency. This research aims to improve the effectiveness of community-based psychosocial rehabilitation interventions for functional disability in schizophrenia.

NIMH supports a program of dissemination and implementation research, with the goal of building the knowledge base on how best to integrate effective mental health interventions into service systems. This research portfolio includes over thirty ongoing studies to better identify the means by which people with mental illness can receive the evidence-based services most likely to alleviate the burden of mental illness and lead to recovery. One recently funded project provided funding to the state of Illinois to determine the best way to implement supportive employment services for people with mental illness returning to the community. Another project is examining factors that improve the statewide implementation of an evidence-based treatment intervention for children in foster care across the state of California, using community development teams to optimize the use of the intervention for children and adolescents in the foster care system. Another study is determining the impact of consumer-run organizations to improve outcomes for individuals with mental illness in communities.

NIMH supports a program of systems research, which focuses on ways in which systems (e.g. criminal justice, schools, welfare) can improve the access to care of persons with mental illness. One NIMH-funded researcher is studying a service system that helps people with mental illness transition from the justice system into a community with services to support their recovery. Another investigator is studying how a nurse manager intervention might improve the health and reduce disability of homeless people with schizophrenia.

COLLABORATIONS WITH SAMHSA ON SERVICES RESEARCH

Question. How is NIMH working with SAMHSA to develop a research agenda focused as much on services research as on clinical trials research?

Answer. NIMH collaborates with SAMHSA on a number of activities to identify key priorities for services research. NIMH continues to collaborate with SAMHSA on research related to the transformation of mental health services in America. The Center for Mental Health Services, (CMHS) within SAMHSA, provides infrastructure support for nine states to collaborate across state agencies to determine how best to transform the delivery of services for people with mental illness. NIMH is supporting the cross-site evaluation of this program—an effort that will facilitate the augmentation of research to the state transformation efforts. In addition, SAMHSA established five interagency priority workgroups to address recommenda-

tions from the Commission Report.³ NIMH and the Agency for Healthcare Research and Quality are working with each of these workgroups to better connect services research to priorities in the areas of emergency response, suicide prevention, employment, financing, and the integration of mental health care and primary care.

NIMH is actively engaged with SAMHSA to generate research based on SAMHSA's major services agendas. An example of this is the research program on "Effectiveness, Practice, And Implementation in CMHS' Comprehensive Community Mental Health Services Program for Children and their Families Service Sites." This three year research effort funds researchers who specifically work within CMHS funded service systems.

NIMH and CMHS have organized a series of Regional meetings for researchers, consumers, policymakers, clinicians, and other key stakeholders to identify research and services needs for state systems. NIMH is also working with CMHS on several meetings to identify the state of the science in specific services areas. The first, on shared decision-making, will bring together expert researchers, consumers, and service providers to discuss the current knowledge base regarding shared decision-making and to develop research priorities. A similar meeting on health promotion for people with mental illness is being planned.

RESEARCH ON SELF MANAGEMENT

Question. In light of the Institute of Medicine's endorsement of the importance of patient-centered mental health care, what is NIMH doing to promote research on models such as illness self-management, patient education, and self-help?

Answer. NIMH has a growing portfolio of research on approaches to improve patient education, self-help, and self-management of mental disorders. NIMH supports a Program Announcement titled "Information Technologies and the Internet in Health Services and Intervention Delivery" to test models of education and self-management for mental disorders.

Current medications used to treat those with chronic and severe schizophrenia often lead to significant metabolic side effects, so a number of NIMH studies are testing models of self-management to promote healthy lifestyles and to reduce diabetes and weight gain in this population. Obtaining evidenced-based care remains a challenge for many individuals with schizophrenia. One study tests an interactive web-based system that allows the individual consumer or family member to compare current treatment to evidence-based standards and to discuss treatment approaches with his or her clinician.

Peer- and community-based programs to support families of adults with serious mental illness typically incorporate elements of self-help, empowerment, trauma recovery, stress and coping theories, as well as mutual assistance for family members. NIMH currently supports several studies to provide scientific evidence that these programs effectively achieve their goals, including for example, the National Alliance for the Mentally Ill's Family-to-Family Education Program—a 12-week class with a highly-structured standardized curriculum developed and conducted by trained family members.

The collaborative care model, developed initially for diabetes medication management, has been successfully applied to depression treatments in primary care. Collaborative care combines patient education about the disorder and its treatment approaches with a depression specialist to assist in case management and treatment adherence. Collaborative care has been shown to be effective in reducing depression and suicidality in older depressed primary care patients, and is currently being studied among women with post-partum depression in two health care plans.

One aspect of patient-centered care is psychoeducation, providing information about mental illness and its long-term care to families and patients. Psychoeducational models originally used with adult patients and their families have been adapted and are currently being tested for use with youth with various mental disorders to strengthen the person's understanding of the illness, to improve treatment adherence, and to facilitate overall illness management. Family-focused treatment as an adjunctive treatment to medication management is being tested with adolescents with bipolar disorder in a three-site clinical trial. An adapted version of this same approach is also being pilot tested with younger youth with mood disorders who are at risk for development of bipolar disorder. A similar approach involved multi-family psychoeducation groups designed as adjunct to medication management was tested for use with families of 8–11 year old youth with mood disorders (depressive disorders or bipolar disorder).

³New Freedom Commission on Mental Health, *Achieving the Promise: Transforming Mental Health Care in America*. Final Report. DHHS Pub. No. SMA-03-3832. Rockville, MD: 2003.

RESEARCH ON FAMILY-BASED TREATMENT PROGRAMS

Question. In light of the disproportional impact of meth on mothers with children, and the continued impact of crack among our poor and urban families, please discuss what research initiatives are being undertaken to recognize and expand the best practices of family-based treatment programs for substance abusing mothers and their children.

Answer. NIDA recognizes the importance of family support as part of drug abuse treatment, particularly for drug-abusing mothers with custody of children. Family therapy that addresses the needs of mothers and that involves their children and other pivotal family members in the treatment program can strengthen and extend program benefits. Findings from research on Brief Strategic Family Therapy (BSFT)—a treatment intervention aimed at adolescents—enforce the benefits of a family-based paradigm to change problem-sustaining family patterns and increase treatment engagement and retention, even in patients with multiple comorbidities.

NIDA supports a variety of research approaches to address the needs of substance-abusing mothers and their children. These include interventions that actively reach out to disadvantaged women at the community level, longitudinal studies that follow children prenatally exposed to drugs, services research to bring evidence-based treatments to the criminal justice system, and clinical research on medications and behavioral treatments in pregnant women and females of childbearing age.

Recognizing the need for culturally-appropriate and gender-sensitive interventions, NIDA-supported researchers are adapting behavioral treatments for substance-abusing female populations, including African American women who abuse crack cocaine, pregnant women in treatment, women with or at risk for HIV, and low-income women in community treatment programs. One study is adapting an empirically based behavioral therapy for drug abuse to a church-based system to intervene with cocaine-addicted African American women, while another is modifying an integrated family behavioral therapy for adolescents to intervene with pregnant women at risk for HIV. Other studies are looking at the quality of maternal-child feeding interactions (during the child's first year) among mothers who used cocaine during their pregnancy, as well as examining the serious risks faced by children exposed to methamphetamine use and manufacture. Results of such studies will help determine how to strategically intervene with mothers and their children.

BETTER TREATMENTS FOR WOMEN IN THE CRIMINAL JUSTICE SYSTEM

Question. Presently, the fastest growing prison population is women convicted of non-violent drug felonies. Most of these women are mothers and most of them are untreated addicts. At the same time, upwards to eighty percent of the families who come to the attention of child welfare are substance abusing. How can we work, or what is NIDA doing specifically, to stop this downward cycle of mothers being displaced into the prison system and children being placed in foster care while the underlying issue of parental addiction remains unaddressed.

Answer. As reflected in the answer to the previous question, NIDA supports research aimed at treating women and mothers with children in the community to prevent their entering the criminal justice system in the first place. These efforts involve a variety of approaches—from adapting evidence-based interventions for use in multiple settings to conducting trials of family-based therapies to using a combination of medications and behavioral approaches to treat drug abusers in the community and help them achieve a healthier lifestyle.

Unfortunately, far too often, drug abuse and addiction remain untreated and escalate to the point of criminal justice involvement, a problem intensifying for females. Indeed, the population of incarcerated women has more than doubled in this country from 1995 to 2005, the problem of female criminal justice involvement characterized by gender-specific factors related to the pathways to substance abuse and recovery, socio-cultural roles and responsibilities, and certain co-occurring mental illnesses. A primary concern for women, which this question addresses, is the greater likelihood of parenting and childcare responsibilities.

NIDA has addressed many of these differences in our recently released landmark publication—principles of Drug Abuse Treatment for Criminal Justice Populations—which conveys effective principles of substance abuse treatment to the criminal justice community and the treatment professionals working with drug-abusing offenders, including women with children. In addition to childcare services, female offenders are more likely than men to need medical and mental health services (given high rates of depression, anxiety, and trauma) and assistance in finding housing and employment. It is important to examine these special needs, for while treatment programs serving both genders can be effective for females, gender-specific programs

may be more effective, particularly for women with histories of trauma and sexual or physical abuse. For female offenders with children, parental responsibilities can conflict with their ability to participate in drug treatment—and yet regaining or retaining custody of their children can also motivate mothers to participate in treatment. Treatment programs may therefore improve retention by offering childcare services and parenting classes.

NIDA is examining these and other methods to make treatments more effective for women, including supporting development of a gender-specific re-entry model to help women reintegrate into the community once released. In addition, a drug court study is looking specifically at ways to improve treatment engagement for women and children. NIDA is also supporting studies of adolescents involved with foster care, identifying the prevalence and heightened risk of substance use disorders among this population. It is worth noting that involvement with foster care is often a marker of prior adversities, including parental addiction, and an antecedent of negative adult outcomes, most of which stem from childhood adversities rather than from foster care per se. In fact, research has shown that therapeutic foster care can be beneficial, particularly to adolescent girls.

VIOLENCE, TRAUMA AND FEMALE DRUG ADDICTION

Question. Please talk about the interrelationship between physical and sexual violence, trauma, and addiction among women, and what research is being done to excavate that interrelationship, especially as it relates to the experience of maternal addiction.

Answer. It is well-established that childhood maltreatment (in the form of sexual abuse, physical abuse, or neglect) leads to enhanced risk for substance abuse, including earlier incidence of alcohol and drug abuse in adolescents. One study has shown that up to 65 percent of the variability in addiction risk is linked to childhood stress; with children who have been subjected to five or more “insults” (i.e., incidents of trauma) being ten times more likely to develop an addiction than those without such exposure. Many of the biological responses to stress have been implicated in the pathophysiology of both substance use disorders and Posttraumatic Stress Disorder (PTSD).

The relationship of substance abuse and addiction to female victimization by sexual violence or other traumatic abuse presents a vicious cycle that can turn both ways, sustained in part by long-lasting negative emotions and behaviors that elicit drug craving and use. Indeed, PTSD and depression are common results of sexual and/or physical abuse and primary risk factors for subsequent drug abuse in females. A multitude of factors influences these events, including age of exposure to physical or sexual abuse, family history, criminal justice involvement, race, co-occurring mental disorders, and other genetic and environmental variables—a tangle of risk factors that NIDA-supported research is investigating to help devise more effective interventions.

Prior research has revealed, disturbingly, that most rape victims (62 percent) are girls under the age of 18, with 28 percent of victims under age 11. This finding reflects the early age at which violence often occurs, and the importance of understanding a person’s history in determining how best to provide treatment. For women, violence more often precedes substance use than the other way around, although both patterns can occur. Thus, treatment that evaluates family history and exposure to violence at various ages might yield important information about chronology of critical variables and relative contributions of environmental and biological factors to comorbid mental and substance abuse disorders.

The effects of trauma are complex and can be manifested in diverse ways. For example, longitudinal and developmental research suggests that girls’ involvement in the juvenile justice system often follows from exposure to trauma and physical or sexual abuse and often co-occurs with anxiety and mood problems. In a recent longitudinal analysis of women who lived in shelters or experienced major violence, study participants had a two-fold increase in their risk of depression over a 6-month follow-up period. And because substance abuse and addiction also significantly increase the risk of subsequent victimization that could lead to PTSD (the reverse direction of the vicious cycle), NIDA also supports studies seeking to add a violence prevention component to substance abuse treatment, particularly for male perpetrators of intimate partner violence. Research on cohabitating substance-abusing patients is offering options to treatment providers who deal with intimate partner violence—40 to 60 percent of couples reporting episodes of partner aggression in the year preceding treatment entry.

Finally, NIDA research has revealed encouraging results for a trauma-focused cognitive behavioral therapy (CBT) known as “Seeking Safety,” designed specifically

for women with trauma histories. Compared to standard substance abuse treatment, the therapy improved both substance abuse and PTSD symptoms in female patients who identified the trauma's effects on their lives and practiced techniques to ease emotional pain, stop self-blame, and cope with difficult interpersonal and potential relapse situations. NIDA is now testing "Seeking Safety" in its National Drug Abuse Clinical Trials Network, which uses "real-world" community treatment programs to validate treatment practicality and effectiveness. This therapy has also shown promising results in adolescent girls, suggesting the need for dual-diagnosis treatment that more directly targets trauma-related symptoms and areas of individual difficulty. Such findings with adolescents are encouraging, as they suggest that comorbid PTSD and substance abuse may be amenable to change early to counter its typical persistence into adult

QUESTIONS SUBMITTED BY SENATOR ARLEN SPECTER
EFFECTS OF PRESIDENT'S BUDGET

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKES

Question. If the President's budget were to be adopted by Congress and research funding were frozen or cut below existing levels, what specific research priorities at your institutes would be delayed or have to be set aside?

Answer. The first priority of NINDS at any funding level is to maintain our existing research commitments, and the President's budget allows us to do that. However, progress against neurological disorders depends on maintaining robust investigator initiated basic, translational, and clinical research programs, and, as you heard in testimony from academic scientists, new and established investigators are struggling. They are spending more time writing and rewriting grant applications than doing research, and too often are forced to drop innovative work, lay off highly trained staff, or close down labs entirely. Under this budget scenario, we would have to reduce or eliminate programs and pass up promising opportunities in order to sustain our core research and ensure that we have a scientific workforce for the future. NINDS would, for example, move fewer promising early phase clinical trials from our SPOTRIAS stroke centers to large phase III trials, move more slowly in developing the Clinical Research Collaboration and Neurological Emergency Treatment clinical trials networks, and not undertake new initiatives, such as applying the model of therapeutics development from the SMA Project to other disorders.

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

Question. If the President's budget were to be adopted by Congress and research funding were frozen or cut below existing levels, what specific research priorities at your institutes would be delayed or have to be set aside?

Answer. With the resources requested in the fiscal year 2008 President's Budget, NIDCD will be able to support its highest priority research. This includes support for a research contract for a multi-center study entitled the "CMV and Hearing Multicenter Screening (CHIMES) Study," on the role of congenital CMV in the development of hearing loss in children. The CHIMES study is one of the largest studies of its kind with approximately 100,000 children to be screened at birth for CMV infection. A major focus of this study is to identify asymptomatic children and follow their progress to determine if hearing loss develops. Those who test positive for CMV will undergo follow-up hearing screening to determine the onset, severity, and progression of hearing loss. If additional funds were to become available to NIDCD beyond these priorities, NIDCD would likely seek to increase the number of children who will be screened for CMV infection.

NATIONAL INSTITUTE OF MENTAL HEALTH

Question. If the President's budget were to be adopted by Congress and research funding were frozen or cut below existing levels, what specific research priorities at your institutes would be delayed or have to be set aside?

Answer. With the resources requested in the fiscal year 2008 President's Budget, NIMH will be able to support its highest priority research. While the President's request did not propose to decrease NIMH's budget, if additional resources became available for NIMH to support research beyond these priorities, NIMH would likely seek to expand its support for in-depth analyses of data collected from whole genome association (WGA) studies for major mental disorders. WGA studies evaluate the subtle differences between the genomes of healthy people and those suffering from disease in order to determine how genetic variability may contribute to disease

susceptibility. In addition to the WGA analyses, NIMH might invest in research to develop new compounds as fast-acting treatments for depression, with the ultimate goal of expanding treatment options so that physicians may offer more personalized care.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

Question. If the President's budget were to be adopted by Congress and research funding were frozen or cut below existing levels, what specific research priorities at your institutes would be delayed or have to be set aside?

Answer. The first priority of NIAAA at any funding level is to maintain our existing research commitments, and the President's budget allows us to do that. In addition, in the fiscal year 2008 Congressional Justification, NIAAA has highlighted a number of promising areas for future research activity. For example, \$3 million have been committed in fiscal year 2008 for research to investigate the short- and long-term effects of alcohol use on the developing adolescent human brain. This funding amount will allow us to conduct pilot studies to determine the best methodology for answering this critical question through future larger longitudinal studies. A second example relates to our funding of medications development. The fiscal year 2008 budget request provides for \$2 million of additional funds for testing compounds and increasing the efficiency of the medications development infrastructure. Whereas it is cost effective to concurrently test multiple compounds, the fiscal year 2008 budget permits sequential testing of a few promising new compounds.

NATIONAL INSTITUTE ON DRUG ABUSE

Question. If the President's budget were to be adopted by Congress and research funding were frozen or cut below existing levels, what specific research priorities at your institutes would be delayed or have to be set aside?

Answer. With the resources requested in the fiscal year 2008 President's Budget, NIDA will be able to support its highest priority research. While the President's request did not propose to decrease NIDA's budget, if additional resources became available to NIDA beyond these priorities, NIDA would likely seek to pursue additional clinical trials and development of new addiction medications; develop a specialized NeuroChip for substance abuse to put in place a single standardized platform for researchers to rapidly screen thousands of an individual's relevant gene variants; support a Genes, Environment, and Development Initiative (GEDI)—a cross-disciplinary initiative designed to increase knowledge of the interactions between genes, environment, and developmental stage in relation to drug abuse risk; and expand NIDA's services research programs operating at the community level, such as its large research collaborations to improve drug abuse treatment for criminal justice populations.

ECONOMIC BENEFITS OF NINDS RESEARCH

Question. Dr. Landis, I am particularly interested cost-savings resulting from NIH research. I understand that NINDS has analyzed the economic benefit of NINDS-supported clinical trials. Could you highlight the results of this study for the Committee?

Answer. At the request of the National Advisory Neurological Disorders and Stroke Council, the institute contracted for an independent evaluation of the costs and benefits of all NINDS phase III clinical trials conducted from 1977 to 2000. The total cost of the clinical trials in the study was \$335 million (adjusted to 2004 dollars). Over 10 years, the benefits from these trials exceeded \$15 billion and added 470,000 healthy years of life to people in the United States. For the entire period of the study, the benefits surpassed \$50 billion, which was greater than the total NINDS budget over that period (\$29.5 billion).

Advances in neuroscience are yielding more clinical trial opportunities than ever before, but trials are expensive and can take years to complete. So, NINDS is now developing computer models to do this kind of analysis prospectively, that is to estimate in advance which trials would have the most impact on public health.

DUCHENNE MUSCULAR DYSTROPHY

Question. Dr. Landis, I understand that NINDS recently funded a large-scale project in translational research for Duchenne muscular dystrophy. Can you tell me about this project, and how it fits into the bigger picture of finding cures for this disease?

Answer. NINDS will soon fund a large-scale project to an investigator at the University of Pennsylvania to develop new small molecule drugs for the treatment of

Duchenne muscular dystrophy (DMD) and potentially other forms of muscular dystrophy as well. DMD is a disease caused by mutations in the dystrophin gene, resulting in a lack of the dystrophin protein. Dystrophin is part of a complex structure involving several other protein components that is required for maintaining proper skeletal muscle structure and function. In the absence of the dystrophin protein, muscle weakening and wasting, and ultimately death, occurs.

The project will pursue a number of strategies for therapy development, including stimulating muscle growth by modulating growth factor pathways, and upregulating proteins that may structurally and functionally substitute for dystrophin or that contribute to the dystrophin protein complex in normal muscle cells. The researchers have already completed a high-throughput screening process on each of these strategies in order to identify small molecules that are candidate therapies. The project will focus on improving the properties of these small molecules as drug candidates and carry out research that will help support further clinical studies using these compounds. One exciting aspect of this project is the fact that a patient voluntary organization (Parent Project MD) as well as a company (PTC Therapeutics) are contributing funds to this project, thereby creating a public-private partnership to leverage funds for this project.

This project is one important component of the larger NIH effort to find cures for DMD and other forms of muscular dystrophy. The Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers also fund translational research aimed at developing therapies for muscular dystrophy. In addition, a few years ago, NIH released a number of initiatives to stimulate translational research in muscular dystrophy, and grants are being funded through these initiatives, as well as through other mechanisms at NIH. A number of strategies for therapy development are being pursued in these studies including gene therapy, cell replacement therapy, enhancing muscle regeneration, and genetic modification strategies. In addition to these translational projects, it is important to note that the mechanistic knowledge obtained through NIH-funded basic research studies has yielded a range of therapeutic targets that NIH-funded research is now pursuing.

SPINAL MUSCULAR ATROPHY

Question. Dr. Landis, can you tell us if any progress has been made toward a treatment for spinal muscular atrophy? What continuing efforts is your institute making in this area? Also please describe the SMA Project, explain what makes it different than the traditional way of doing translational research at NIH, and comment on how it might serve as a model for research on other diseases.

Answer. The goal of the SMA Project is to bring at least one new drug for SMA to readiness for clinical testing as quickly as possible. The project uses a performance-based contract. It is quite different from the usual way we do research because of the central direction and the way it is organized. A project steering committee, with extensive expertise in drug development from industry and the FDA, as well as from the NIH, put together a detailed drug development plan and is heavily engaged in guiding progress. The project is implementing the plan via a "virtual pharma organization" that develops and brings together all of the necessary resources through subcontracts to companies that serve the drug development industry.

The Project has put more than 800 compounds through repeated cycles of modification and evaluation in laboratory tests and is making encouraging progress. Some of these potential drugs show dramatically improved potency and efficacy in simple laboratory tests, and NINDS gathered sufficient data to file a patent application in March 2007. In 2007 and 2008, the most promising compounds will advance through more definitive tests of effectiveness in mice that have been genetically engineered to mimic human SMA. By June of 2007, the project intends to select a clinical candidate and begin the preclinical safety studies that will support clinical testing. We are already applying lessons from the SMA Project for other disorders through a similar contract mechanism planned for this year that will address a major barrier to drug development by providing access to medicinal chemistry services.

We are also continuing other lines of SMA research in both the extramural and intramural programs. This year, for example, intramural researchers collaborating with Italian scientists showed for the first time that a drug treatment could be effective in an animal model of SMA when treatment is begun after the symptoms of disease have already appeared, which is an encouraging finding.

STEM CELLS

Question. Dr. Landis, you serve as the Chair of the NIH Stem Cell Task Force. What steps would NIH take to implement S. 5, the Stem Cell Research Enhancement Act of 2007?

Answer. If the bill were to be passed, a panel of experts would need to be immediately convened to develop and issue guidelines for implementation. NIH's experience in implementing human embryonic stem cell (hESC) research the past years would be vital in developing these new guidelines. In addition, NIH would develop a format for reporting requirements mandated within sections 2 and 3 of the act.

CLINICAL TRIALS

Question. Dr. Insel, when Dr. Zerhouni was here last week, he noted that to continue to support ongoing research projects and allow for new investigators to successfully apply for support, it has been necessary to reduce support for clinical trials research. Has this also affected your institute? Will you be able to continue important clinical trials?

Answer. NIMH is providing infrastructure support to maintain three large networks of investigative clinical teams that have evolved from the recent NIMH practical clinical trials on major depressive disorder, schizophrenia, and bipolar disorder. The networks comprise over 60 sites throughout the United States with continual outreach and engagement to diverse groups of patients and families with mental illnesses. NIMH plans to support research studies that utilize the resources established by these networks; these studies must be of significant public mental health importance, provide value to individuals living with mental illnesses and to practitioners, and incorporate input from broad scientific and public domains. Under the President's Budget request, NIMH would be able to support a few studies on these clinical trial networks.

Other recent NIMH-funded research has led to several promising new pharmacological treatment approaches for mental disorders. For example, a recent study uncovered a new mechanism of action to target for the fast relief of depression. In addition, NIMH has supported a large research effort focused on identifying novel compounds for treating the cognitive deficits associated with schizophrenia. NIMH hopes to build on these research findings to develop new compounds as fast-acting treatments for depression and as cognitive enhancers for those diagnosed with schizophrenia. Under the President's Budget request, NIMH would support a limited number of trials to test the efficacy of these promising new compounds.

ECONOMIC BENEFITS OF MENTAL HEALTH RESEARCH

Question. Dr. Insel, can you tell us about the economic benefits that have resulted from investment in mental health research?

Answer. Mental disorders are associated with enormous economic burdens. The President's New Freedom Commission on Mental Health estimated that these economic costs are on the order of \$150 billion each year in the United States alone.⁴ Much of this cost is due to the lost work productivity that results from mental illness. A large body of NIMH-supported research indicates that much of this economic cost, including that derived from impaired work performance, could be alleviated by standard treatments for mental disorders. Yet, the cost of mental illness persists in part because of widespread underuse and the poor quality of implementation of treatments that have been shown to be efficacious and tolerable. Recent effectiveness trials supported by NIMH have shown that a variety of models that enhance the care of mental disorders through aggressive outreach and improved quality of treatments are highly effective at improving clinical outcomes, and in some cases, on work performance outcomes as well. Economic analyses accompanying these effectiveness trials have also shown that these quality improvement interventions are cost-efficient. Unfortunately, widespread uptake of these enhanced mental health treatment programs has not occurred due to barriers at the level of providers, health care systems, and purchasers of health care. Additional ongoing research supported by NIMH is examining how to most effectively overcome these barriers to high-quality mental health care and to ultimately reduce the enormous adverse economic impact from mental disorders.

⁴New Freedom Commission on Mental Health, *Achieving the Promise: Transforming Mental Health Care in America*. Final Report. DHHS Pub. No. SMA-03-3832. Rockville, MD: 2003.

HEARING LOSS

Question. What recent progress has been made toward better treatments for partial and full hearing loss? Has there been any specific progress in better hearing aid technology?

Answer. Approximately 28 million Americans have a hearing impairment. Hearing loss is one of the most prevalent chronic health conditions in the United States, affecting people of all ages, in all segments of the population, and across all socioeconomic levels. It affects approximately 17 in 1,000 children under age 18. Incidence increases with age: approximately 314 in 1,000 people over age 65 have hearing loss. Because of the immense public health need, for over 30 years, the NIH has played a significant and important role in sponsoring the development of cochlear implant technology. The cochlear implant is the only sensory neural prosthesis in widespread clinical use and according to the Food and Drug Administration's 2005 data; nearly 100,000 people worldwide have received implants. In the United States approximately 22,000 adults and nearly 15,000 children have received them. Continued research on ways to assess how well current users benefit from their cochlear implants will enable scientists to design implants that will be more effective for all future implant users. Some individuals with severe to profound hearing loss are receiving a cochlear implant for each ear. Research is demonstrating that these dual implant users are significantly better at localizing sounds and hearing speech in a noisy room, when compared to individuals with a single implant. Scientists also are developing a new cochlear implant electrode designed to provide electrical stimulation of the auditory nerve for high-frequency sounds while preserving useful, residual hearing at low frequencies. Scientists can now study the large groups of newborns who are identified for hearing loss and use this knowledge to document how cochlear implants can lead to improved speech acquisition, academic performance, and economic outcomes for these children.

While cochlear implants bypass damaged portions of the inner ear and directly stimulate the auditory nerve, hearing aids amplify sounds. Scientists are determining which individuals can most benefit from hearing aids and the best ways to select and fit hearing aids in children and other people whose hearing ability is difficult to test. One of the most exciting advancements in hearing aid technology resulted from NIH-supported research. The discovered technology is based on the ears of a parasitic fly, *Ormia ochracea*. Despite their small size and the short distance between them, *Ormia's* ears are able to rapidly pinpoint the location from which the sound of a potential host—a cricket—is coming, even in a noisy environment. The intriguing mechanism that enables *Ormia* to accomplish this feat has provided a model for scientists and engineers to use in developing miniature directional microphones for hearing aids that can better focus on speech in a single conversation, even when surrounded by other voices. This finding has revolutionized the technology used for directional microphones and will improve the quality of life for the million of individuals with hearing impairment.

Scientists are continuing to develop treatments for hearing loss that can be tailored to individuals' unique needs. The combined use of a hearing aid and a variation of the cochlear implant is another treatment being explored. A hearing aid in one ear combined with a shortened electrode array inserted into a portion of the cochlea of the other ear have proven to be effective in allowing individuals with hearing loss in the high frequencies to improve hearing. More research needs to be done to determine which individuals should receive these combined devices and which devices yield the most benefit. Researchers continue to conduct studies to determine the age at which hearing aids provide maximum success in early language development.

BASIC RESEARCH AND HEARING

Question. Please give us an example of how basic research into the mechanics of hearing has led to better patient outcomes. Why is basic research important in the areas covered by your institute?

Answer. Hearing aid users want devices that enable them to better understand speech. Two recent surveys demonstrate this desire. Poor benefit in noisy situations was listed among the top 20 reasons why hearing aid owners don't use their hearing aids. Another survey of 2,428 hearing aid owners found that improved understanding of speech in noise was among the top 10 desired changes. Of all the available technologies, directional microphones for hearing aids have shown the most promise for addressing this problem, as demonstrated by clinical studies of individuals with hearing loss.

Because of basic research, NIH-supported scientists successfully completed a fabrication process to miniaturize the prototype of a low-power, highly directional hear-

ing aid microphone so that it will fit into a hearing aid. This directional microphone mimics the auditory system of the parasitic fly, *Ormia ochracea*. The fly's system is an excellent model to imitate because its mechanically coupled ears enable it to detect the direction of sound and because it suggested a way to miniaturize a microphone for use in hearing aids. The scientists used silicon microfabrication technology to make a directional microphone that is small enough to be incorporated into a hearing aid. The directional microphone developed in fiscal year 2006 will ultimately help hearing aid users to better understand speech in a noisy background, such as in a crowded room. The microphone is able to do this by giving more weight to sound originating closest to the ear.

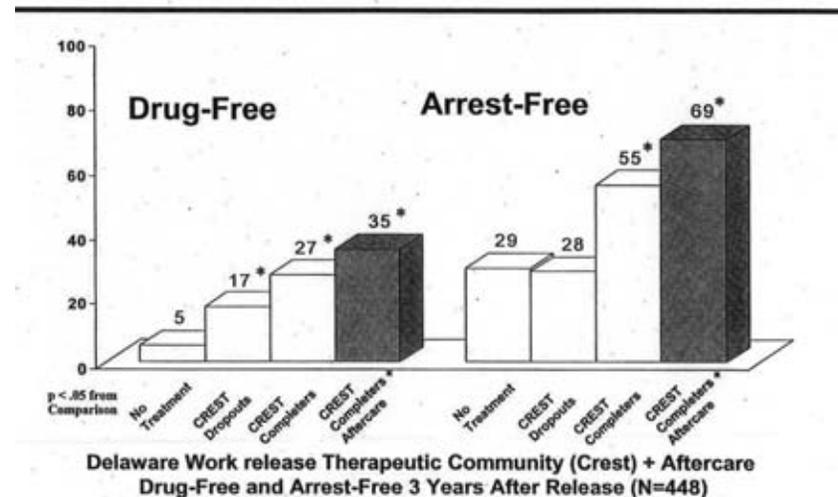
This is an excellent example of why basic research is so important. Basic research often relies on studies in "model organisms," such as mice, fruit flies, or bacteria. Because human cells contain the same molecular building blocks and pathways as those of most other living things, researchers can learn much about the way our cells work by studying these simpler organisms. These models allow scientists to design and control their experiments tightly and to select the type of organism best suited for examining a specific problem or process. The ability to conduct basic research on the ears of *Ormia*, has revolutionized the technology used for directional microphones and will improve the quality of life for millions of individuals with hearing impairment. This is one of the many examples of advances that grew out of basic research. In conclusion, while basic research studies do not always have an immediate impact on our health, such research often leads to new medicines, technologies, and research tools.

DRUG ABUSE TREATMENT

Question. Dr. Volkow, I understand that your Institute has released principles of drug abuse treatment for criminal justice populations. Could you please summarize for us how you recommend dealing with drug abuse treatment for criminal populations?

Answer. NIDA's recently released booklet, Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research Based Guide, reflects NIDA-supported research aimed at improving outcomes for offenders with substance abuse problems. The principles emphasize the need for customized strategies, which can include behavioral therapies, medication, and consideration of other mental and physical illnesses. The key message is that drug abuse treatment works, especially with community involvement and support, and brings about reduced drug abuse, criminal recidivism, and relapse to addiction.

Treatment Reduces Drug Use and Recidivism



For that reason, treatment is cost-effective: for every dollar spent on drug abuse treatment an estimated \$4–\$7 in benefits ensues from avoided criminal justice costs—benefits that grow as addiction treatment continues over time. Data also

show that treatment can work even when it is entered involuntarily. NIDA therefore recommends that treatment for criminal justice offenders be part of a continuum of care that begins in prison and continues throughout the difficult periods during and following re-entry into the community.

To help ensure better outcomes for offender populations, NIDA recommends an integrated approach that cuts across multiple public health and public safety systems. In this vein, NIDA launched a Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) Initiative, a multisite and multiagency research initiative to focus on implementing new research-based drug abuse treatment models in the criminal justice system. And because effective interventions may include pharmacotherapies, or medicines for drug abuse and addiction, NIDA recommends their use in criminal justice settings as part of a comprehensive treatment regimen—which will necessitate a culture change.

Another tenet of effective drug abuse treatment is a proper balance of rewards and sanctions to encourage prosocial behavior and treatment participation. It is important to reinforce positive behavior for those participating in drug abuse treatment, with sanctions applied gradually, in line with degree or persistence of non-compliance.

To effect needed changes, NIDA will continue to reach out to judges and others in the criminal justice system to educate them about the behavioral and biological aspects of addiction through intensive training workshops. We will also continue to support studies examining ways to make quality treatment options available through drug courts and other alternatives to incarceration for substance abusers.

ADDICTION AS A BRAIN DISEASE

Question. Dr. Volkow, I understand that many in the field of drug abuse research strongly argue that addiction is a brain disease. Do you agree with this assessment, and if so, why?

Answer. Yes, I wholeheartedly agree that addiction is a brain disease. Decades of scientific research by NIDA and others have affirmed drug addiction as a disease that alters the brain in ways that affect behavior. The compulsive craving, seeking, and use of drugs, even in the face of dire life consequences, happens because addiction affects the same brain circuits that are also involved in reward, motivation, memory, and control over behavior. And when these are usurped by drugs, so is a person's capacity to freely choose not to use drugs, even when it means losing everything they used to value. In fact, the inability to stop is the essence of addiction.

Brain imaging and basic neuroscience research have helped us to understand how drugs of abuse alter brain function. We depend on our brain's ability to release dopamine in order to experience pleasure and to motivate responses to the natural rewards of everyday life, such as the sight or smell of food. Drugs of abuse produce very large and rapid dopamine surges and over time the brain responds by reducing normal dopamine activity. Eventually, the disrupted dopamine system renders the addict much less sensitive to pleasure—even to the drugs they seek to feed their addiction. Drugs of abuse also affect the regions of the brain that help people control desires and emotions, as evidenced by brain imaging research in humans revealing changes in the functions of these circuits. Thus, drug addiction affects the very brain areas that people need to “think straight,” apply good judgment, and make good decisions for their lives. The resulting lack of control leads addicted people to compulsively pursue drugs, even after the drugs have lost their effectiveness in producing pleasure; for now even the memories that are linked to the drug motivate behaviors to seek the drug. Behavior becomes reflexive and much less amenable to cognitive interference. Just as the damaged heart can no longer propel the blood to our bodies, the damaged brain can no longer propel the nerve impulses to control desires and emotions.

Like any other medical disorder that impairs the function of vital organs, repair and recovery of the addicted brain depends upon targeted and effective treatments that address the complexity of the disease. Brain imaging shows recovery as well. Research is proving new insights on how this can be done. NIDA is engaged in studying new scenarios for what constitutes effective treatment: pharmacological treatments to mitigate stress and prevent relapse, cognitive treatments that strengthen the frontal (thinking) part of the brain, and strategies that diminish conditioned responses, promote new learning, inhibit stress-induced relapse, and restore the rewarding experiences from natural reinforcers.

UNDERAGE DRINKING

Question. Dr. Li, how is your institute addressing the growing problem of underage drinking? Is progress being made?

Answer. Although the problem of underage drinking persists progress is being made:

(1) Based on converging evidence from multiple fields we now know that underage drinking is best addressed and understood within a developmental framework because this behavior is directly related to processes that occur during adolescence. Using such a framework will make us more effective in preventing and reducing underage alcohol use and its associated problems.

(2) This paradigm shift along with recent advances in the fields of epidemiology, developmental psychopathology, human brain development, and behavioral genetics provided the scientific foundation for the Surgeon General's recently released Call to Action to Prevent and Reduce Underage Drinking, the work of the Interagency Coordinating Committee on the Prevention of Underage Drinking (ICCPUD) and the work of its member federal agencies and departments.

(3) The release of the first ever Surgeon General's Call to Action on underage drinking is a landmark event which will heighten awareness of the problem in all sectors of society.

(4) Federal surveys indicate some modest declines on certain measures of underage drinking. While this progress is encouraging, the prevalence of underage drinking, and especially binge drinking, remain high.

(5) In order to better characterize trends in underage drinking in America, information beyond that previously available from national surveys is needed. Based on NIAAA's recommendations, new questions on patterns of drinking (e.g. very high level consumption, sources of alcohol, and drinking venues) are now being included in national surveys.

(6) A key research question is the extent to which adolescent drinking impacts the developing human brain. Research with rodents and studies with alcohol dependent youth suggest that alcohol use during adolescence, particularly heavy use can have deleterious short- and long-term effects on the developing brain. To further address this central scientific question, NIAAA has released a Funding Opportunity Announcement for two-year pilot studies in this area entitled The Impact of Adolescent Drinking on the Developing Brain. Successful applications in response to this announcement will be funded in fiscal year 2007. These studies are expected to inform a larger longitudinal initiative.

ALCOHOL AND CANCER

Question. Dr. Li, I understand that drinking alcoholic beverages has been linked to an increased risk of several types of cancer. Could you please tell us if this link has been confirmed, and if so do we know what the mechanism for the link might be?

Answer. Chronic alcohol consumption is a well-established risk factor for cancer of the oral cavity, pharynx, esophagus, and larynx. For example, for those individuals who average 100 grams of alcohol consumed per day (about 7 standard drinks) the relative risk for cancer of the oral cavity and pharynx increases 6.5 times compared to non-drinkers. Consuming this same level of alcohol increases the relative risk for cancers of the larynx, esophagus, breast and liver 3.9, 3.6, 2.4, 1.8 fold respectively. While not as high, there are also significant elevated risks for each of these cancers associated with consumption of 25 grams of alcohol per day (about 2 standard drinks). Concurrent smoking and drinking, which is common, synergistically increases the risk of cancer. For example, one study reported an 18-fold increase in the relative risk for esophageal cancer due to the consumption of more than 6 drinks/day, a 5-fold increase due to smoking more than 20 cigarettes/day, and 44-fold greater risk for combined heavy alcohol consumption and cigarette smoking.

Alcohol is metabolized primarily by alcohol dehydrogenase in the liver to form acetaldehyde, a highly reactive and carcinogenic compound which is further metabolized by aldehyde dehydrogenase (ALDH2) to acetate. A variant of this enzyme (ALDH2*2) is virtually inactive (leading to higher concentrations of acetaldehyde) and occurs in 28–45 percent of Asian populations. As a result of the accumulation of acetaldehyde, homozygous carriers of this allele (ALDH2*2/*2) experience aversive reactions to alcohol including strong facial flushing and toxic reactions. Therefore most homozygous individuals either abstain or drink infrequently. In contrast, heterozygous carriers (ALDH2*1/*2, which has about 10 percent residual ALDH2 activity) who consume alcohol are at a high risk for developing esophageal cancer. Thus, acetaldehyde is implicated as a carcinogen, and is included in the list of "IARC Group 2B Carcinogens." Several mechanisms have been implicated in alcohol-induced cancer, including: (1) formation of acetaldehyde which forms adducts with DNA; (2) production of reactive oxygen species (ROS) and lipid peroxidation

products; (3) changes in folate and methionine metabolism; (4) alcohol-induced increase in estrogen formation in breast cancer; (5) suppressed immune function; and (6) alcohol's solvent action enhancing the bioavailability of carcinogens from tobacco and other sources. The induction of microsomal cytochrome P450 enzymes by alcohol increases the metabolism of procarcinogens, such as nitrosamines, present in tobacco smoke, and likely plays an important role in the greater risk for cancer due to heavy alcohol consumption and smoking.

SUBCOMMITTEE RECESS

Senator HARKIN. So with that, thank you very much.

The subcommittee will stand in recess to reconvene at 9:30 a.m., Wednesday, March 28, in room SD-124. At that time we will hear testimony from the Honorable Elaine L. Chao, Secretary, Department of Labor.

[Whereupon, at 5:24 p.m., Monday, March 26, the subcommittee was recessed, to reconvene at 9:30 a.m., Wednesday, March 28.]