

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Mind, Brain, and Behavior

**Witness appearing before the
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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 (FY) 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 U.S. 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 momentum 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.