DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

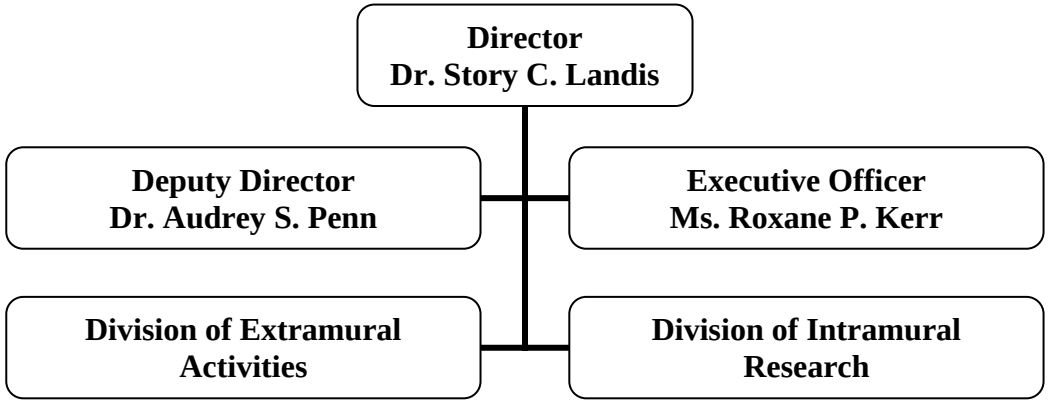
National Institute of Neurological Disorders and Stroke

FY 2007 Budget	Page No.
Organization chart	2
Appropriation language	3
Amounts available for obligation	4
Justification narrative	5
Budget mechanism table	28
Budget authority by activity	29
Summary of changes	30
Budget authority by object	32
Salaries and expenses	33
Significant items in House and Senate Reports	34
Authorizing legislation	72
Appropriations history	73
Detail of full-time equivalent employment (FTE)	74
Detail of positions	75
New positions requested	76

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Organizational Chart



NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

For carrying out section 301 and title IV of the Public Health Service Act with respect to neurological disorders and stroke, [1,550,260,000]*$1,524,750,000*.

[Department of Health and Human Services Appropriations Act, 2006]

National Institutes of Health
National Institute of Neurological Disorders and Stroke

Amounts Available for Obligation 1/

Source of Funding	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Appropriation	$1,552,123,000	$1,550,260,000	$1,524,750,000
Enacted Rescissions	(12,675,000)	(15,503,000)	0
Subtotal, Adjusted Appropriation	1,539,448,000	1,534,757,000	1,524,750,000
Real transfer under NIH Director's one-percent transfer authority for Roadmap	(9,732,000)	(13,715,000)	0
Comparative transfer from OD for NIH Roadmap	9,732,000	13,715,000	0
Subtotal, adjusted budget authority	1,539,448,000	1,534,757,000	1,524,750,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	1,539,448,000	1,534,757,000	1,524,750,000
Unobligated balance lapsing	(62,000)	0	0
Total obligations	1,539,386,000	1,534,757,000	1,524,750,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2005 - $10,969,000 FY 2006 - $12,125,000 FY 2007 - $12,125,000
Excludes $225,000 in FY 2006 and $662,000 in FY 2007 for royalties.

Justification
National Institute of Neurological Disorders and Stroke

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act, as amended.

Budget Authority:

FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
531	$1,539,448,000	549	1,534,757,000	552	1,524,750,000	3	-$10,007,000

This document provides justification for the Fiscal Year 2007 activities of the National Institute of Neurological Disorders and Stroke, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2007 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)." Detailed information on the NIH Roadmap for Medical Research may be found in the Overview section.

Introduction

The mission of the NINDS is to reduce the burden of neurological disease through research to improve prevention and treatment. Stroke, traumatic brain injury, dementias, chronic pain, epilepsy, neuropathies, brain tumors, Parkinson's disease, multiple sclerosis, spinal cord injury, amyotrophic lateral sclerosis (ALS), and hundreds of other disorders of the brain, spinal cord, and nerves of the body collectively affect all age groups, and every segment of society. Together, disorders of the nervous system, common and rare, cause an enormous burden in lost life, disability, and suffering, as well as costing billions of dollars each year in medical expenses and reduced productivity.

Prevention and treatment of neurological disorders are still far from adequate, but progress is improving life for many people. Because of many incremental advances over the last few decades, hundreds of thousands of strokes are prevented each year. Emergency stroke treatment is also now available that can improve the outcome for some people. Better drugs and surgical treatments reduce symptoms from Parkinson's disease, epilepsy, chronic pain, dystonia, multiple sclerosis, and many other neurological disorders. Advances in brain imaging and in genetic testing also enhance physicians' ability to diagnose and treat neurological disease. As the largest supporter of research on neurological disorders, the NINDS has contributed significantly to this progress.

To accomplish its mission, the NINDS supports research to understand the nervous system in health and disease, to translate that knowledge into strategies for prevention and treatment, and to evaluate interventions in clinical trials. The Institute's extramural program supports research through grants and contracts to physicians and scientists at medical schools, hospitals, universities, private research institutions, and small businesses throughout the country. These investigators seek out scientific opportunities, propose research projects, evaluate study

proposals in peer review, carry out research, and advise the Institute on planning for the future. NINDS intramural investigators conduct research on the NIH campus in Bethesda, Maryland. The NIH campus provides one of the largest communities of neuroscientists in the world. Among its unique resources, the Mark O. Hatfield Clinical Center is a hospital totally dedicated to clinical research and the NIH Neuroscience Center is explicitly designed to integrate neuroscience across disciplinary boundaries. In keeping with its mission, the NINDS also supports the training of scientists and physicians and provides reliable information to scientists, physicians, government, and the public.

Science Advances

The prospects for better prevention and treatment for neurological disorders are encouraging. New ideas for interventions arise from clinical studies and from basic research on the healthy and diseased nervous system. Studies of how the nervous system develops revealed the potential of stem cells to repair the nervous system and of natural "neurotrophic" factors that may protect from neurodegeneration. Research on how the brain controls movement paved the way for deep brain stimulation to relieve symptoms of essential tremor and Parkinson's disease. Better understanding of brain circuits may allow similar treatment for dystonia, Tourette syndrome, and epilepsy. Studies of learning and brain plasticity are yielding surprising insights into chronic disorders, such as dystonia and chronic pain, as well as inspiring behavioral interventions that stimulate the brain's latent capacity to recover from damage. Genetic studies are the source of therapies, now under development, to repair or replace defective genes in inherited neurological diseases and to provide therapeutic genes in non-inherited chronic pain, Parkinson's, and other disorders. Gene research has already produced clues about what causes disease, identified key molecular targets for drugs, improved diagnostic tests, and produced animal models of human disorders for testing of therapies. Whatever the source of an idea, researchers refine their basic understanding in the laboratory, develop therapeutic interventions in cells and experimental animals, and evaluate safety and effectiveness through clinical trials. The NINDS supports research at every step of this process. The Institute's research, especially in basic neuroscience, also provides an essential foundation for efforts against neurological diseases in the private sector. The following examples from the thousands of findings published in the past year by NINDS supported investigators illustrate the range of ongoing research.

Preventing recurrent stroke: People who have intracranial stenosis--partially blocked arteries in the brain--have a high risk of stroke. The results of a double-blind, randomized clinical trial this year provide important information for preventing strokes in people who have intracranial stenosis and have had a non-disabling stroke or a transient ischemic attack (TIA, or mini-stroke). For this group, aspirin is safer and prevents stroke as well as warfarin, a drug that requires expensive monitoring, careful dose adjustment, and carries the risk of side effects from bleeding.

Human neural stem cells promote recovery in spinal cord-injured mice: Researchers have improved movement and agility in spinal cord injured mice by transplanting human neural stem cells. Importantly, the investigators were able to determine what the cells did after transplant, a critical step for advancing stem cell biology toward human therapies. To do so, after allowing the cells to act for up to 17 weeks, the investigators killed the transplanted cells with a toxin that affects human cells, but not mouse cells. Thus, they were able to identify the dying transplanted cells and evaluate their contributions to recovery. The transplanted cells survived for at least 17

weeks before they were intentionally eliminated. The cells migrated away from the transplant site, produced cells called oligodendrocytes that restore the insulating covering (myelin) of nerve fibers, and also generated nerve cells and synapses that improved the ability of the mice to move.

Drug reverses learning disability in mice: Neurofibromatosis type 1 (NF1) is among the most common genetic disorders that affect the nervous system. In addition to producing tumors and other structural deformities, NF1 is associated with a spectrum of disabilities in learning and attention. Following the discovery of the gene defects that cause NF1, researchers generated mice that mimic the human disorder. By studying these mice, investigators identified a biochemical pathway affected by the gene that basic studies had shown is critical for learning. A new study has found that the drug lovastatin, which interacts with this biochemical pathway, can reverse the learning disabilities in NF1 mice. Lovastatin is a common and well tolerated drug used to control cholesterol.

Insights into neurodegeneration from SCA1 flies and mice: Spinocerebellar ataxia (SCA1) causes progressive loss of motor coordination and balance. This disease is one of at least eight inherited disorders caused by an abnormal repetition of part of the genetic code. That repetition in the gene in turn leads to abnormal repeats of the protein building block glutamine in the protein chain produced from the affected gene. How the glutamine repeats cause the different patterns of nerve cell loss in each glutamine repeat disease was not known. New findings from studies of SCA1 mutant flies and mice show that the mutation slows the breakdown of ataxin-1, the protein affected in SCA1. The researchers showed that too much of even the normal ataxin-1 protein kills specific types of nerve cells by its effect on the regulation of other genes. The idea that too much of a protein, rather than aberrant actions of a protein, can lead to neurodegeneration may also apply to other neurological disorders, including Alzheimer's, Parkinson's and Down syndrome, in which a toxic protein is implicated.

Protecting the brain from HIV: There has been dramatic progress in controlling the HIV virus in the body. However, most antiretroviral drugs do not cross the blood-brain barrier, so the virus, which does enter the brain, often causes neurological problems despite appearing to be under control. By studying a closely related virus, SIV, in non-human primates, scientists found that the antibiotic minocycline can protect the brain in an animal model of HIV disease. The drug not only reduced inflammation and protected brain cells, but also reduced replication of the virus in the brain. The NINDS, through the NIH Neurologic AIDS Research Consortium, is supporting the development of a clinical trial to follow up this finding. The Institute also has an ongoing solicitation on the use of SIV and other models for studying HIV in the nervous system.

Motor neuron development: Motor neurons in the spinal cord take on many specialized identities that direct their connections with muscles. This allows precise movement control. By studying the development of the chick nervous system, scientists have unraveled how 39 genes called the Hox gene family generate the diverse types of motor neurons, their position in the spinal cord, and their connections. Hox genes are a focus of intense interest because they control the activity of other genes and thereby regulate development in organisms from fruit flies to people.

Exercise and Parkinson's disease: According to a new study, men who exercised vigorously as young adults had a 50% lower risk of developing Parkinson's disease in later life than men who

had low levels of physical activity. This correlational study cannot distinguish whether exercise lowers the risk of Parkinson's disease, or men who develop the disease are somehow predisposed to avoid exercise early in life. However, the convergence of epidemiological data with results of animal experiments increasingly suggests that exercise may promote brain health, in addition to its other well documented health benefits.

Treating seizures in newborns: Seizures in newborns are difficult to treat because infants do not respond well to the drugs used to treat seizures in adults. In adults, these drugs enhance the actions of the neurotransmitter GABA, which suppresses brain electrical activity, but in infants GABA actually does the opposite—it excites nerve cells. Scientists have determined that the developmental difference in GABA actions arises from the way the ion chloride is transported into and out of immature nerve cells. They showed in human infants that chloride transport changes over the first year of life to approach the levels found in adults. By using a known diuretic drug, called bumetanide, which acts on chloride transport, the investigators effectively treated seizures in newborn mice. Bumetanide has been used safely in infants for other purposes and may be useful in the treatment of seizures of newborns, if clinical trials confirm this finding.

Generating brain and spinal cord neurons: Researchers have developed a step-by-step procedure that coaxes human embryonic stem cells in cell culture to generate motor neurons, the nerve cells in the brain stem and spinal cord that activate muscles. The procedure relies upon natural signaling molecules identified through decades of fundamental studies of nervous system development. Another line of research builds on the finding that the brains of even adult mammals, including humans, can generate new nerve cells to a limited degree. New research shows that under appropriate circumstances the brains of adult mice can replace corticospinal neurons. These anatomically elaborate nerve cells control voluntary movement via very long nerve fibers they extend from the brain to the spinal cord. Stimulating the formation and growth of motor neurons and corticospinal neurons may someday allow repair of damage from traumatic injury and neurodegenerative diseases. The ability to generate specific nerve cell types in cell culture may also be useful tools for screening drugs.

Drug therapy for brain tumors: Glioblastoma is a common and deadly type of brain tumor, and treatments are far from adequate. As for lung cancer, a small proportion of patients with glioblastoma appear to respond to a new class of drugs called EGFR inhibitors. By identifying the molecular mechanism by which these drugs work in glioblastoma, researchers have developed a way to test tumor samples and predict which patients will benefit from these drugs.

Silencing harmful genes: In 1990, scientists attempting to generate deep purple petunias by manipulating a pigment gene found white flowers instead. After a decade of follow up research, we know that a phenomenon called RNA interference, or RNAi, was responsible for the white flowers. RNAi is a widespread, but previously unrecognized, regulator of gene activity in plants, invertebrates, and mammals. The mechanism of RNAi is based on the classic DNA matching code—a short RNA molecule matches up with a complementary segment of DNA and silences activity of the specific gene. Scientists, in separate investigations, have now used RNAi to selectively silence the harmful genes in mouse models of spinocerebellar ataxia, Huntington's disease, and an inherited type of ALS. RNAi may be widely applicable to dominantly inherited

diseases, those in which a harmful gene inherited from either parent causes disease. The NINDS is supporting continued research to move RNAi therapy toward readiness for testing in people.

Controlling brain plasticity: Nerve cells in the young brain adapt to experience or to injury by changing their functional connections with other nerve cells. Why the mature brain loses much of this "plasticity" is a mystery. Now scientists have provided compelling evidence that a particular brain protein, called the nogo receptor, contributes to the loss of plasticity. When researchers developed strains of mice that lack the nogo receptor, the brains of the mice retained plasticity beyond the normal age at which plasticity is lost. Nogo and its receptor first captured attention as a factor limiting regeneration in the damaged spinal cord. Perhaps the normal role of nogo may be to help stabilize brain circuits after development.

Zeroing in on gene loci for neural tube defects: Neural tube defects, including spina bifida and anencephaly, are among the most common and serious birth defects. Supplementing vitamin B9 (folate, or folic acid) in women can reduce the occurrence of neural tube defects by 50 to 70%, but even women who take the recommended amount of folic acid may have a child with a neural tube defect. Genetic influences are at least partly responsible. A consortium of dozens of investigators from 14 centers nationwide, studying 292 individuals from 44 families, has now completed the first full genetic analysis of families with neural tube defects. The analysis located regions on chromosomes 7 and 10 that are likely to contain relevant genes, and regions on chromosomes 11, 15, and 21 that may also be involved. This is a major step towards finding specific genes that predispose towards neural tube defects.

Toward a "bladder pacemaker": Loss of bladder control from spinal cord injury or other neurological disorders adversely affects quality of life and can lead to life threatening urinary tract infections and kidney damage. A team of researchers has demonstrated that nerve cell circuits in the spinal cord itself can coordinate the activity of the bladder and urethral sphincter to achieve normal bladder emptying, and that nerve stimulation can activate this reflex. With this new understanding of normal bladder control, it is feasible to design a "bladder pacemaker" that will restore control of bladder emptying and incontinence for people with spinal cord injury or other neurological disorders. Work toward this goal is underway.

Dyslexia genes: Dyslexia is a very common learning disability. People with dyslexia have normal intelligence but impaired ability to read. Based on a study of 153 families, researchers have identified a defective gene (DCDC2) that may be implicated in as many as 20% of people with dyslexia. The gene defect appears to affect the development of brain areas that are involved in reading. Recently, researchers in Germany and the United Kingdom have also identified genes that may be involved in dyslexia. Although understanding how genes affect a complex skill like reading is extremely challenging, together these findings may ultimately lead to improved understanding and to better diagnosis, so that children can get help earlier to overcome their problems with learning to read.

Preventing cerebral vasospasm: An intracranial aneurysm is a localized weakening of a blood vessel in the brain that balloons out and can rupture, causing bleeding in the brain. When rupture occurs, about half of the people who reach the hospital and are successfully treated subsequently develop cerebral vasospasm, a sudden constriction of brain blood vessels that can lead to

disability or death. Research in primates now shows that the drug sodium nitrite prevents cerebral vasospasm. Sodium nitrite increases nitric oxide, which basic studies had identified as a natural signal controlling blood vessels. Whether this drug is as effective in people, who may have unstable heart and brain conditions, must be determined in clinical trials.

Rejuvenating old muscle: To investigate why muscle, liver, and other tissues regenerate much better in younger than older individuals, scientists linked the blood circulation of young and old mice. The experiments showed that a chemical factor in the circulation of the young mice enhanced tissue repair by stem cells that reside in muscle and liver of the older mice. The results imply that muscle and liver stem cells in old mice must retain a capacity to regenerate. Identifying the blood factors from the young mice might lead to new treatments for muscle disease and other disorders.

Gene therapy for neuropathic pain: Damage to nerves from disease or injury often provokes chronic neuropathic pain, which is notoriously difficult to treat. Researchers have now alleviated neuropathic pain in rats for up to 6 weeks via gene therapy. In this treatment, a harmless version of a herpes virus delivered a gene for the enzyme that synthesizes the neurotransmitter GABA. Previous studies had shown that GABA, which reduces the electrical activity of nerve cells, is deficient in neuropathic pain. Because the virus's natural route of infection goes through the body's nerves to the spinal cord, using the virus is an effective way to deliver therapy precisely to the spinal cord where it may reduce pain with minimal adverse effects.

Astrocytes and epilepsy: In epilepsy, bursts of synchronized activity among groups of nerve cells in the brain provoke recurrent seizures. Astrocytes, the supporting cells in the brain that maintain a hospitable environment for nerve cells, are known to passively react to seizures. New research shows that astrocytes can also actively provoke seizure activity in the brain. Focusing on astrocytes may provide a way to control seizures with less suppression of normal nerve cell activity and reduced side effects, or even to prevent epilepsy from developing in the first place.

Delivering genes to treat muscular dystrophies: One of the biggest challenges in developing gene therapy for muscular dystrophies is delivering beneficial genes widely to muscle cells throughout the body. Now, researchers have shown in rodents that a virus called adeno-associated virus 8 (AAV8) can effectively deliver a gene to skeletal muscles and to the heart. In a hamster model of limb-girdle muscular dystrophy, delivery of the delta-sarcoglycan gene corrected the degeneration and other problems normally seen in this disease. Similarly, after delivery of the gene agrin, the body weight of mice that mimic a severe form of congenital muscular dystrophy improved by 80% at 6 weeks of age, and the mice lived about four times as long as untreated mice. A next step in this research is to study AAV8 gene delivery in dogs with Duchenne-like muscular dystrophy to learn if the treatment is effective in larger animals.

Detecting Prions in blood: The public health importance of the rare neurological diseases called Transmissible Spongiform Encephalopathies (TSEs) has increased dramatically. First, evidence arose that an animal form of TSE, bovine spongiform encephalopathy (mad cow disease) can be transmitted to people. More recently, there are indications that TSEs may be transmissible through transfer of blood products from people with TSEs. Better detection of TSEs is thus a high public health priority, but the unusual nature of TSEs precludes use of the usual methods to

diagnose infectious disease and detect blood contamination. By understanding how rogue proteins called prions propagate in TSEs, researchers have developed a method to amplify the low level of abnormal prions in blood of experimental rodents more than 10 million fold and detect the prions with conventional protein detection methods. Work is underway to apply this method to other animals and to humans. In addition to improving the safety of the blood supply and surveillance of cattle, therapies are more likely to work the earlier TSEs can be diagnosed.

Gene associated with Tourette syndrome: Tourette syndrome is a neurological disorder characterized by repetitive, stereotyped, involuntary movements and vocalizations called tics. Several decades of research suggest that there is a substantial genetic contribution to Tourette syndrome, but no responsible gene defects had been identified. Researchers have now identified defects in a gene that can cause Tourette syndrome. Basic developmental studies have previously studied the gene, called SLITRK1, because of its role in guiding growing nerve fibers in the developing brain. Although this particular gene may account for a small percentage of Tourette syndrome cases, the finding is a starting point to study the underlying changes in the brain that lead to the disease and to develop better therapies.

Rescuing fragile X flies: Fragile X syndrome is a common inherited cause of mental retardation that is associated with a variety of other psychiatric and neurological symptoms. Building on the discovery of the gene defect responsible for the syndrome, scientists developed fruit flies with a similar gene defect. These flies have abnormalities that are reminiscent of the human disorder. Studying these flies led to a theory that implicates changes in a particular brain neurotransmitter system in fragile X. That theory has now led to the finding that the drug lithium or drugs called metabotropic glutamate antagonists can reverse the short term memory deficits, behavioral problems, and structural changes in the brains of these flies.

Brain computer Interfaces—a story of discovery

Benjamin Franklin was intrigued by the notion that electricity, judiciously applied, might coax paralyzed muscles to move. Almost two hundred and fifty years later, electrical devices on the market or in testing aid breathing, bowel and bladder function, hand grasping, and even standing for people who are paralyzed. Most dramatically, a new generation of "brain computer interfaces" (BCI) tap directly into the brain. Experimental BCI devices have enabled rats, monkeys, and even a few people to activate a lever, move a robotic arm, or control a computer just by thinking about it.

One type of BCI detects brain waves from outside the head via electrodes on the scalp. Scientists discovered more than 30 years ago that people can learn to control their brain waves, which arise from the summed electrical activity of millions of brain cells. NINDS-supported researchers and their colleagues in Germany have devised ways to translate brain waves to movement of a computer cursor. With practice, people can control a cursor well enough to answer about four yes or no questions in a minute. Using an "adaptive algorithm," by which a computer program learns from each trial, people can even control a cursor in two dimensions. Patients who are conscious but severely paralyzed by ALS, strokes, or brain trauma may be among the first to benefit from this technology.

The other major approach to BCI requires that electrodes be implanted in the brain to monitor neuron activity associated with arm and hand control. This method is invasive, but is more likely to yield the rapid, precise signals necessary to control a prosthetic limb or robotic device. Using electrodes implanted in the cerebral cortex, NINDS-supported researchers have demonstrated that rats can activate a mechanical lever and monkeys can control a computer cursor or a virtual arm in a computer generated 3-dimensional environment. Most recently, researchers have shown that signals from a monkey's cortex can be monitored, analyzed, and translated

quickly enough to control a robotic arm that mimics the actions of the monkey's real arm, a major step toward control of a fully functional prosthetic arm.

More than 100 years ago, by studying brain damaged patients, neurologists inferred which areas of the brain control movement. Over the last century, thousands of studies advanced that understanding. NINDS-supported basic research in the 1980's directly inspired BCI devices by showing that a "population vector" calculated from the activity of a few dozen brain neurons precisely predicts—and presumably could also control—limb movements. As intensive research continues toward fostering recovery from brain and spinal cord damage through regeneration and plasticity, neural prosthesis research and regeneration research complement one another. Neural prosthetic techniques may stimulate regeneration and plasticity, and plasticity of brain neurons contributes to BCI performance.

Although basic research laid the groundwork, BCI and other neural prostheses also require engineering and applied research that integrates across several disciplines. For more than 35 years, the NINDS Neural Prosthesis Program has been a major catalyst for this research. The program supports biomaterials scientists who work with experts in brain tissue to develop implantable electrodes that can reliably perform in the brain for months at a time without doing harm. Experts in micro-fabrication techniques design tiny implantable multi-electrode arrays that detect signals from many neurons simultaneously. Electronics engineers and computational scientists develop methods to rapidly extract useful information from those complex and faint signals. Over the years, research teams supported by the program have contributed to the development of cochlear prostheses for hearing impaired people, and to nerve and muscle stimulation for bowel and bladder control, respiratory control, grasping, standing and walking, as well as to BCI. A major goal for this program is to integrate BCIs with neuromuscular stimulation systems to enable a paralyzed individual to voluntarily control his or her own limb movement. Improving deep brain stimulation (DBS) for Parkinson's disease and other movement disorders has also become a major focus of the program.

Research is continuing toward making BCI and other neuroprosthetics safe, fully implantable, and reliable enough to meet the needs of people. Today, the NINDS Neural Prosthesis Program works together with NIH Institutes that were established since the program began. The National Institute on Deafness and Other Communications Disorders (NIDCD) focuses on auditory neuroprostheses. The National Center for Medical Rehabilitation (NCMRR) Research, within the National Institute of Child Health and Human Development (NICHD), has an interest in applications to rehabilitation. The National Institute of Biomedical Imaging and Bioengineering (NIBIB) promotes technology development. The NIH investments in nanotechnology, computational science, and interdisciplinary studies, through the Roadmap and other programs, are also directly relevant. As the field has progressed, the Department of Defense has begun a major program to produce a next generation of BCI-based prosthetic limbs to meet the needs of soldiers who have experienced amputation. Within the private sector, venture capitalists are now staking their money on an emerging BCI market and expansion of clinical applications of DBS.

Although Ben Franklin did not apply electricity effectively to paralysis, he did invent one assistive device that is still popular today (bifocals). As a scientist, inventor, and one of the fathers of our independence, he would approve of bringing together diverse areas of science and technology to promote independence for people with paralysis from stroke, spinal cord injury, traumatic brain injury or neurodegeneration.

The NIH Roadmap

The challenges of neurological disorders have always pushed the frontiers of medical science, so it is perhaps not surprising that more than half of the 2005 Roadmap Pioneer Awardees pursue research related to the nervous system. Historically, integration across diverse areas of science and engineering has also driven neuroscience. Thus, another aspect of the Roadmap that aptly illustrates its impact on the NINDS mission is the Roadmap's enhancement of interdisciplinary research. Several of the National Centers for Biomedical Computing have obvious potential for advancing neuroscience, and two centers bring together teams specifically for developing computational tools to understand changes in the brain during health and disease. Similarly, Roadmap Exploratory Centers for Interdisciplinary Research are developing new directions for

stroke rehabilitation and for understanding how the brain influences the body during systemic diseases, and the Roadmap supports an interdisciplinary network focused on novel assessment and interventions for pain. Building for the future, Roadmap interdisciplinary initiatives support cross-cutting training in neurodevelopmental toxicology, neurobehavioral development, autism, regenerative medicine, computational neurosciences, and neuroengineering.

The NIH Molecular Libraries and Imaging Roadmap Initiative illustrates how the Roadmap complements the Institutes' mission-specific programs. This Initiative broadens access to advanced technologies for finding chemicals that target important biological mechanisms, via the automated testing of thousands of chemical compounds in assays (laboratory tests) of biological processes. Active compounds identified through this high-throughput screening (HTS) process provide starting points in the design of pharmacological probes for studying key biological mechanisms and can be used to establish the role of a molecular target in a disease process. The NIH established nine Roadmap Molecular Libraries Screening Centers in 2005 to provide HTS access. PubChem, a database and website under the leadership of NIH's National Center for Biotechnology Information, will make the chemical structural information and findings from Screening Center activities easily available to the scientific community in a central resource.

NINDS leads an essential component of the Molecular Libraries Roadmap Initiative, the development of assays for biological processes that can be screened within the Molecular Libraries Screening Centers Network. Assay development and implementation "primes the pump" in Roadmap efforts to create molecular probes for pharmacological investigation. Emphasis is on screening of targets that may be key points to intervene in rare diseases. In 2005, 38 projects were funded in this program, and 10 have a direct relevance to the NINDS mission. The Roadmap is collecting more than 500,000 small molecules for use by the Screening Centers Network. This resource complements NINDS efforts to create a Brain Institutes Bioactive Compounds Library, consisting of chemicals with likely nervous system-specific activity.

New Initiatives

NINDS initiatives target public health needs and scientific opportunities that are not adequately addressed by unsolicited investigator-initiated research. Some initiatives provide scientific resources that accelerate the research of many individual investigators. Others focus on diseases or research questions that are underserved. In developing initiatives, the NINDS consults with the scientific, professional, and patient communities and seeks guidance from the Congressionally mandated National Advisory Neurological Diseases and Stroke (NANDS) Council. Many initiatives respond to disease-specific research plans or critical issues raised at scientific workshops on diseases, scientific areas, or technologies.

NINDS develops all initiatives within the framework of a strategic plan. The Institute last developed a strategic plan in 1999, and science has moved rapidly. So, in fiscal year 2006, the Institute will begin renewing its strategic plan. The plan will guide the Institute in balancing research on the hundreds of neurological disorders, common and rare, within its mission; across the many areas of basic, translational, and clinical research that are essential to progress; and between short term opportunities for modest progress and long-term goals of preventing and curing diseases. The Institute will engage all stakeholders in this process.

The NINDS is planning the following new or expanded initiatives for fiscal year 2007:

NINDS Human Genetics Repository: The NINDS Human Genetics Repository acts as a national resource for the discovery of genes relevant to neurological disorders. In 2003, the NINDS established the repository to collect, store, characterize, and distribute DNA samples and cell lines, as well as associated clinical data, for the research community. As of June 2005, the repository had collected material from 6828 unique subjects, including stroke (2460), epilepsy (617), Parkinson's disease (2103), and motor neuron diseases, including ALS (50), as well as control samples (1517). The collection is ethnically diverse and represents populations from Asia, South America, and Europe, as well as the U.S. More than a dozen scientific articles have already been published or are undergoing review based on data from this resource. With the extension of the facility for another five years, the resource will add another disease, Tourette syndrome. As the Repository continues to collect samples, there is increased emphasis on distribution of samples to investigators and on increasingly sophisticated database needs to coordinate with other resources, including, for example, clinical trials and the Morris K. Udall Centers of Excellence in Parkinson's Disease Research. The progress in the HapMap and increasing attention to gene-environment interactions and to pharmacogenomics also enhance the value of the repository as a resource for the scientific community.

Medicinal chemistry for neurotherapeutics: The NINDS will expedite the translation of basic discoveries into drugs for neurological disorders by removing a major barrier in the drug development process—the lack of access to resources for optimizing lead compounds via medicinal chemistry.

Drug development requires multiple stages. First, researchers screen large numbers of chemicals in simple, rapid laboratory tests to find "lead compounds." Lead compounds are chemicals that have some degree of desired effect but are not adequate to use as drugs because of insufficient potency, undesirable side effects, or lack of drug-like characteristics, such as solubility and absorption into the brain. In the next stage, researchers chemically optimize lead compounds. That is, medicinal chemists systematically modify the lead compounds, and investigators test for improved characteristics, until the process generates candidate compounds with genuine potential as drugs. Following chemical optimization, the best drug candidates move on to extensive preclinical testing for safety and effectiveness in animals. Finally, clinical trials demonstrate safety and effectiveness in people.

Over the last several years, the NINDS and the NIH Roadmap have developed programs for screening to find lead compounds, for preclinical testing, and for clinical trials. However, limited access to the medicinal chemistry resources for chemical optimization remains an obstacle for neurological therapeutics researchers outside of large pharmaceutical companies. The NINDS SMA Project, a pilot project to develop a drug for SMA, has developed a contract approach to provide resources for chemical optimization. Based on that experience, the NINDS will use a similar mechanism to provide medicinal chemistry for promising lead compounds for other neurological disorders. As with the SMA Project, a steering committee with experience in drug development from industry, the NIH, and the FDA will guide the program.

Epilepsy models for pediatric and aged populations: The highest incidence of epilepsy occurs in children and in the elderly. Current animal models do not adequately address the special considerations for developing drugs for epilepsy in the developing brain and the aged brain. In children, for example, intractable epilepsies and catastrophic epilepsies associated with developmental brain abnormalities present special problems, and anti-seizure drugs may act differently than in the mature brain. Among the elderly, who constitute the fastest growing population experiencing seizures, stroke, trauma, and neurodegeneration can contribute to epilepsy. Issues related to drug absorption and clearance and to drug interactions are also significant for these groups. The NINDS has convened scientific workshops focused on the development of animal models of pediatric epilepsy and will hold a workshop in 2006 on models of epilepsy in the elderly. Following the guidance of these groups, the Institute will request applications for the development of animal models of epilepsy in children and in the elderly. These models will be an important component of NINDS programs to develop more effective treatments with diminished side effects through the NINDS Anticonvulsant Screening Program (ASP) and other research efforts. The Institute has used a similar approach to develop better models for treatment resistant epilepsy and for preventing the development of epilepsy.

GENSAT--Gene Expression Nervous System Atlas: Understanding where and when genes are active is key to understanding how the healthy nervous system develops and works and what goes wrong in disease. More than half of all genes are active at some point in the brain, yet only a small fraction of these have been well characterized. To systematically address this issue, in 2000 the NINDS initiated the GENSAT project. The first stage of the project uses a prescreening procedure called *in situ* hybridization to examine the activity of large numbers of genes at 4 developmental time points in several parts of the brain and spinal cord. Based on the prescreening, investigators more thoroughly examine a smaller number of genes of high interest using BAC (bacterial artificial chromosome) technology. The BAC method generates strains of mice in which a visible marker is turned on wherever and whenever the gene of interest is active. These mice allow scientists to classify, observe, and track brain cell types according to molecular characteristics and function, and are very useful for answering many scientific questions.

As the current GENSAT contract is renewed, the project will build on the substantial success to date. The prescreening phase met its original target of examining 600 and 1100 genes per year in the last two years, and the rate will increase to 1500 per year in order to reach the goal of mapping 10,000 genes by 2011. The BAC component also reached its target of 250 genes per year, which will increase to 300 per year. GENSAT will create an additional 25-50 mouse strains each year via an advanced technology that allows genes to be turned on and off at will to study their function. The rapidly growing database of information generated by GENSAT has already become a valuable and heavily used resource for the scientific community. The project is also responding to hundreds of requests from researchers throughout the country for the BAC mouse strains, which are a valuable resource for many types of neuroscience research.

Angiogenesis in health and disease: The brain and spinal cord are more dependent than any other organs on a continuous supply of oxygen and nutrients from the blood. Angiogenesis—the formation of new blood vessels— contributes to recovery from stroke and trauma, and defects in angiogenesis have been observed in neurodegenerative disease. However, relatively little is

known about angiogenesis in the brain and spinal cord. The NINDS will solicit research proposals in this understudied area.

Neuroprotective Immunomodulation: Inflammation is the immune system's first response to injury and plays a critical role in many diseases, including heart disease, cancer, and stroke. There is increasing evidence that the immune system can contribute to the progression of disease or help protect the brain from harm in brain tumors, ALS, Alzheimer's disease, brain and spinal cord trauma, and many other neurological disorders, as well as in multiple sclerosis and infection, in which the role of the immune system has long been recognized. Some drugs now used to protect against stroke, including aspirin, act at least partly by modulating immune system activity, and experimental therapies based on active immunization (similar to vaccination) have shown considerable promise in animal experiments. To stimulate this understudied area of research, the NINDS will solicit research proposals with an emphasis on interdisciplinary collaboration. The goal is to learn how to protect the brain by modulating the immune system.

The NIH Neuroscience Blueprint: The NINDS is actively engaged in the NIH Neuroscience Blueprint, which brings together NIH Institutes and Centers that support research on the nervous system. The first Blueprint initiatives, released in FY 2005, include an inventory and analysis of neuroscience tools, enhancement of training in the neurobiology of disease for basic neuroscientists, and expansion of programs in genome analysis and in neuroimaging. Blueprint initiatives for FY 2006 are developing training programs, genetic mouse models, neuroimaging tools, core research facilities, and tools to assess neural function that will enhance the value of clinical research conducted by each Blueprint institute for the missions of all. In FY07, the Blueprint will focus on neurodegeneration—the progressive death of nerve cells—which contributes to many diseases of the nervous system. Following discussions with the scientific community, Blueprint initiatives will focus on tools and resources that will help investigators tackle barriers to progress and exceptional opportunities in neurodegeneration research.

Other Areas of Interest

Because science advances quickly, NINDS programs must have the scope and flexibility to respond to new needs and opportunities as they arise. For this reason, programs that support investigator initiated research constitute the major part of NINDS activities. The Institute tailors specific programs to support basic research, to translate basic research insights to therapies, and to expedite clinical trials. Many of these ongoing activities stimulate scientific collaboration, sharing, and common resources. Other continuing NINDS programs focus on training, on minority health and health disparities, and on dissemination of information to the public and the medical community. As with new initiatives, continuing programs reflect priorities identified through strategic and disease specific planning efforts. The following highlights a few ongoing NINDS activities:

Clinical research and clinical trials: The NINDS currently supports more than 1000 extramural and intramural research projects that involve human subjects. Of these, more than 125 are clinical trials of interventions to prevent or treat neurological disorders. Clinical trials projects range from planning, through pilot trials and early phase investigations, to large multi-center studies to test the safety and effectiveness of interventions. Interventions now under study include drugs, natural biological molecules, surgery, deep brain stimulation, hypothermia,

oxygen therapy, radiation, immunotherapy, and behavioral therapies. New or ongoing trials focus on disorders including ALS, ADHD, brain tumor, cerebral palsy, epilepsy, headache, Huntington's disease, multiple sclerosis, muscular dystrophy, myasthenia gravis, pain, Parkinson's disease, spinal muscular atrophy, stroke, Tourette syndrome, and traumatic brain injury. In addition to clinical trials, other clinical studies provide essential information that may lead to better treatment and prevention strategies. Projects include, for example, epidemiological investigations of risk factors for stroke among Blacks and Hispanics, brain imaging investigations in healthy children and those recovering from brain damage, and investigations of gene defects that contribute to common and rare neurological disorders. As one indication of the scope of NINDS clinical research programs, more than 300,000 people are expected to participate over the course of studies that are now underway.

The NINDS clinical trials program has made major contributions to improving public health. In stroke, for example, Institute trials developed t-PA therapy, the only FDA approved emergency treatment to improve outcome, and made substantial contribution to stroke prevention. To respond to increasing opportunities, the Institute has developed a comprehensive program to enhance clinical trial design, peer review, data management, and monitoring. The clinical trials program is putting increased emphasis on improving practices with regard to potential conflicts of interest and on developing common data elements that will enhance the efficiency and effectiveness of the clinical research enterprise. Training is also an important avenue to improve the reliability and effectiveness of clinical trials. Programs under development will introduce clinical fellows and junior faculty to the principles of good clinical trial design; expose early career clinical scientists to the full spectrum of challenges in clinical research; and develop a cadre of well-trained, experienced clinical researchers. Broadening training opportunities for researchers and future community practitioners is essential not only for the conduct of clinical trials itself, but also to hasten the introduction of improved regimens for therapy and prevention of neurological disorders into everyday medical practice and patient care.

The development of clinical trials networks is a major ongoing activity. Networks will improve the speed and efficiency of trials, access for participants, and adoption of results by practicing physicians. Networks include:

- The NINDS Pilot Studies Network (NPTUNE), which expedites pilot trials for rare diseases that lack the infrastructure to effectively organize trials. After a systematic review of candidate trials for rare neurological diseases, NPTUNE selected for its first trial an investigation of the drug phenylbutyrate for spinal muscular atrophy (SMA).

- The Clinical Research Collaboration (CRC), now under development, which will engage hundreds of community practice-based and academic-based neurologists to speed trials, minimize costs, make trials more accessible to patients, recruit a diverse spectrum of participants, enable more trials of rare diseases, and improve the transfer of research results to clinical practice in community settings.

- The Emergency Neurological Clinical Trials Network (ENCTN), which will focus on stroke, head and spinal cord trauma, status epilepticus (continuous seizures), and other neurological emergencies, which constitute a significant percentage (5 to 10%) of all medical emergencies

and often cause long term disability. This network will engage experts in emergency medicine, neurology, neurosurgery, and clinical trials design to confront the special challenges of clinical trials for these emergencies.

Translational research: Translational research encompasses the many steps that move promising basic research findings to practical therapies with sufficient evidence of safety and effectiveness to justify clinical trials. In 2002, the NINDS developed a comprehensive translational research program, and in 2005 the Institute renewed the program with increased efforts to engage small businesses. The NINDS Cooperative Program in Translational Research, Exploratory-Developmental Projects in Translational Research, and Cooperative Small Business Awards in Translational Research solicit proposals to develop treatments for any disease within the Institute's mission. As with all NINDS programs, the proposals are rigorously peer reviewed. The expertise and criteria of review are tailored to the objectives of translational research. The NINDS closely monitors progress, with milestone-driven funding. This program explicitly fosters collaborative research, which is critical for therapy development. New and ongoing projects are developing drug, stem cell, or gene therapies for Batten disease, Parkinson's disease, Huntington's disease, tuberous sclerosis, Duchenne muscular dystrophy, traumatic brain injury and stroke, among other disorders.

In 2005 the NINDS also funded a center whose experts in drug development will help post-doctoral scientists transform basic biology discoveries into drugs for neurodegeneration. The center will take on 5 new projects each year and up to 25 projects over the 5 years of the program. With the renewal of the NINDS translational program, the Institute has solicited proposals for other Translational Research Resource Centers that will provide products and services that will expedite the development of interventions for neurological disorders.

Targeted NINDS activities in translational research complement the broad translational research program. Examples include:

The Anticonvulsant Screening Program (ASP): The ASP catalyzes academic and industry efforts to develop drugs for epilepsy by screening candidate drugs in a series of standardized cell culture and animal models. This rigorous program of testing and analysis provides information about the effectiveness, mechanisms, and pharmacological properties of candidate drugs. Since 1975, the ASP has screened more than 26,000 drugs from more than 400 academic and industry partners in 31 countries. More than 40 drugs from this program have entered clinical trials, including several now on the market, and 7 more that are currently in clinical development. The ASP is placing increasing emphasis on drugs to prevent epilepsy, for treatment resistant epilepsy, and for pediatric and geriatric populations.

The SMA Project: The SMA Project is making encouraging progress towards its ambitious goal of having a drug for SMA ready for clinical trials by the end of 2007. The steering committee, with expertise in drug development from industry, the FDA, academia and the NIH, has developed a detailed drug development plan. The project has identified compounds that have sufficient effectiveness in SMA model systems and appropriate chemical characteristics to serve as leads for developing a drug. The project has also established the tools and facilities for systematically modifying these leads, testing the newly generated drug candidates in cell and

animal models, handling the substantial informatics requirements, and coordinating the overall drug development scheme. The drug development process is now underway, with more than 300 new compounds already synthesized.

The Neural Prosthesis Program: The Neural Prosthesis Program aims to develop devices that compensate for nervous system function lost through injury or disease. Over the past 35 years, this program has made substantial contributions to the development of technology for cochlear implants, improved respiratory assist devices, hand grasp prostheses, deep brain stimulation, and other devices. Current work ranges from efforts to restore voluntary bowel and bladder control and standing to spinal cord injured persons, to technologies that will allow paralyzed persons to control devices through direct control from their brains.

Collaborative research and common resources: Understanding how the brain and nervous system work, what goes wrong in disease, and how to prevent or treat these disorders requires scientists from many disciplines. For this reason, the NINDS supports researchers not only in basic disciplines of anatomy, physiology, biochemistry, cell biology, genetics, systems biology and behavior, and in clinical neurology, neurosurgery, and brain imaging, but also in physics, chemistry, engineering, biomaterials, and computational sciences. Even traditional single investigator grants often build research teams with varied expertise, and joint research projects among laboratories with synergistic capabilities are the norm in today's scientific environment. The Institute, through a variety of programs, stimulates multiple investigator efforts in basic, translational, and clinical research. Many NINDS Initiatives are cooperative efforts with other parts of the NIH, and, when appropriate, with other groups including the National Science Foundation or private organizations. The Blueprint for Neuroscience and the NIH Roadmap are also vehicles to address issues that transcend a single Institute. A few examples of NINDS programs illustrate some of the ways in which the Institute provides common resources, stimulates collaborative research, and enhances opportunities for sharing among scientists:

Intramural program: The goal of the National Neuroscience Center is to "put the brain back together." This first phase of this facility, which opened in 2004, brings together 50 scientists from 8 Institute and 5 buildings in an environment designed to foster cross-fertilization of ideas via shared facilities, animal models, expertise, specialized neuroscience tools, and research fellows. The design is working. For example, this year, an NINDS intramural laboratory, collaborating with extramural scientists, identified a gene for a motor neuron disorder. They quickly collaborated with researchers from the National Institute on Aging to develop a mouse model of the disease and with investigators from the National Institute of Child Health and Human Development to develop a cell culture system to study the gene.

Microarray Consortium: Gene microarrays allow scientists to monitor simultaneously the expression (activity) of virtually all genes in the brain. Studies of gene expression yield clues about how the normal brain develops and adapts, what goes wrong in disease, how therapies work, and which patients will respond. In 2002, the NINDS and the National Institute of Mental Health (NIMH) established a consortium of three microarray centers to make this technology and the necessary expertise available to their researchers and to make data from array studies available to the scientific community. In 2005 this consortium expanded to serve scientists supported by all NIH Neuroscience Blueprint Institutes. The Consortium now has more than

1000 registered users and has completed more than 130 projects requiring nearly 5000 arrays. Studies have focused, for example, on diseases that include Alzheimer's, autism, brain tumor, epilepsy, Huntington's, spinocerebellar ataxia, and stroke, and on scientific questions about stem cells, brain plasticity, and regeneration.

Center core grants: Center core grants provide shared resources to groups of NINDS grantees. The grants provide resources to support basic, translational, and clinical research, and these joint facilities foster an interactive research environment and stimulate inter-disciplinary approaches to neuroscience research. Cores includes resources for specialized light and electron microscopy, animal models of human disorders, informatics and statistics, proteomics, DNA sequencing, and brain imaging. Beginning in 2006, NIH Neuroscience Blueprint is supporting a program of larger grants for core resources that will allow other technologies beyond what single Institutes can support and may serve multiple institutions.

Mouse sharing: Genetically modified strains of mice are essential for understanding the brain and for developing therapies. Several NINDS planning groups highlighted the need to improve access to these mouse models, which require considerable time, expertise, and cost to generate. The Institute, and NIH generally, have taken several steps to encourage sharing. Most recently, the NIH began requiring grantees to include a sharing plan. In 2002, as one element of these efforts, the NINDS began providing supplemental funding to cover the costs of sharing. To date, this program has made 160 mouse models available to more than 500 laboratories.

Centers and multi- investigator grants: The NINDS supports multi-investigator teams via program project grants, centers, and contracts. Some of these collaborative efforts are investigator initiated and others respond to targeted solicitations focused on specific needs. Current projects focus on stroke, traumatic brain injury, epilepsy, multiple sclerosis, HIV dementia, multiple sclerosis, neurofibromatosis, autonomic dysfunction, narcolepsy, pain, Huntington's disease, brain tumor, Alzheimer's disease, spinal cord injury, dystonia, prion diseases, brain vascular malformations, neuromuscular disease, migraine, and multiple system atrophy, as well as on scientific issues including nervous system development and stem cells.

Cross-Institute NIH efforts: The NINDS works closely with other NIH Institutes and Centers on many specific programs in addition to the NIH Roadmap and the NIH Blueprint for Neuroscience. Ongoing cooperative programs focus, for example, on basic neuroscience training, pediatric neuroimaging, pain, neuroAIDs, cognitive and emotional health, autism genetics, muscular dystrophy, international training and research, rehabilitation, development of therapies for stroke and for brain tumor, bioengineering research, microarray centers, autoimmune diseases, and the development of genetics and genomics resources, including the human HapMap Project and other genomics resources.

Disease specific plans: Over recent years, the NINDS has engaged hundreds of scientists from government, academia, and industry, and representatives of non-governmental organizations in planning research for specific diseases. The NINDS website (http://www.ninds.nih.gov/about_ninds/ninds_plans.htm) provides the Parkinson's Disease Research Agenda and Matrix; the Epilepsy Benchmarks; the Brain Tumor and the Stroke Progress Review Groups (PRGs); the Five-Year Strategic Plan on Minority Health Disparities;

the Research Plan for Tuberous Sclerosis Complex (TSC); and the Muscular Dystrophy Research and Education Plan. Development of a research plan for ataxia telangiectasia is underway. The Institute also participates in NIH planning and implementation for autism, HIV-related research and autoimmune disease, and attends to Institute of Medicine reports on spinal cord injury, multiple sclerosis, transmissible spongiform encephalopathies, and other diseases. Finally, the NINDS receives guidance from many scientific workshops each year. Recent and planned meetings focus on ataxias, hydrocephalus, neuropathies, HIV dementia, vascular cognitive impairment, muscular dystrophy, epilepsy, triplet repeat disorders, and stroke. Many of these meetings and plans are cooperative efforts among NIH Institutes and Centers. Ensuring coordination among the parts of NIH is a major goal whenever there is a shared interest in neurological disorders. A few examples illustrate NINDS implementation of recommendations from disease planning:

Stroke: In 2001, the NINDS convened 150 stroke experts in the Stroke Progress Review Group (PRG) Roundtable to identify gaps in knowledge and set research priorities. Since then, the NINDS has undertaken dozens of programs, initiatives, and workshops that respond to priorities identified in the PRG report. The NINDS and the National Heart Lung and Blood Institute (NHLBI) have an active stroke working group, and many stroke programs represent cooperative efforts. The six SPOTRIAS (Specialized Program of Translational Research in Acute Stroke) are an important element of the Stroke implementation, and the NINDS renewed the program in 2005. The SPOTRIAS translate basic research findings into clinical practice, conduct clinical trials of acute stroke treatments, develop clinical tools for rapid treatment, evaluate rehabilitation strategies, identify biomarkers, improve brain imaging, increase stroke awareness, and train new investigators. The SPOTRIAS act as a network through a common clinical database, collaborations on research, sharing of resources, and regular meetings. Another key resource, the NINDS Human Genetic Resource Center, provides DNA and cell lines for study of stroke genetics. Grant solicitations are another important element of implementation efforts, with recent examples focused on neuroprotective barriers, reducing stroke disparities, neurovascular mechanisms, vascular cognitive impairment, and novel therapies. Recent scientific workshops have addressed racial and ethnic disparities in stroke, improving access to treatments for stroke patients, priorities for clinical research on treatment of hemorrhagic (bleeding) stroke, genetics of vascular cognitive impairment, pediatric stroke, and on stroke risk assessment and primary prevention. Research in the active NINDS Intramural stroke program includes vaccine approaches to stroke prevention, brain imaging for stroke diagnosis, and novel emergency stroke therapies. Stroke centers at Suburban Hospital in Bethesda, Maryland and Washington Hospital Center, in the District of Columbia, are an important aspect of these intramural programs efforts.

Parkinson's disease: The NINDS developed the NIH Parkinson's Disease Research Agenda in 2000. Since then, the NIH has periodically engaged the research and patient community in reviews of progress, scientific discussions of specific issues, and priority setting, most recently in the 2nd Parkinson's Disease Research Summit convened by the NIH and NINDS directors in June 2005. In response to the original Agenda, and the continuing discussion of developing opportunities, the NIH has initiated extensive programs to develop drug therapies, surgical interventions including deep brain stimulation, gene therapy, and cell transplantation therapies. These efforts include the Deep Brain Stimulation (DBS) Consortium and a major clinical trial of DBS in cooperation with the Department of Veterans Affairs, a consortium of researchers to

develop gene therapy, translational research projects in stem cells, high throughput drug screening for drug development, and the Neuroprotection Exploratory Trials in Parkinson's disease (NET-PD), which is a program of clinical trials of drugs to slow the progression of Parkinson's disease. Through investigator initiated research and targeted initiatives, the NIH is also funding extensive research to better understand the causes and treat the motor and non-motor symptoms of Parkinson's disease. The Morris K. Udall Parkinson's Disease Research Centers of Excellence are an integral part of these efforts, and the NINDS has expanded the clinical activities of the centers. Extensive details of the full range of NIH Parkinson's disease activities are available on the Parkinson's Disease Research Web at: http://www.ninds.nih.gov/parkinsonsweb/index.htm .

Epilepsy: In March 2000, the NINDS organized the conference "Curing Epilepsy: Focus on the Future" in cooperation with several patient advocacy groups. The meeting began a planning process that brought the scientific and patient communities together with NINDS to identify seventeen specific research goals. These "Benchmarks for Epilepsy Research" measure progress towards a cure for epilepsy, defined as "no seizures, no side effects." Through investigator initiated research, scientific workshops, initiatives, and the NINDS Anticonvulsant Screening Project, the NINDS is addressing priorities that include finding better drugs for treatment resistant epilepsy, preventing the development of epilepsy, and improving drugs for the pediatric and geriatric populations. Activities also include collection of DNA samples for study of genes in epilepsy, microarray studies of gene expression, and development of better animal models. Ongoing clinical trials address issues including depression in epilepsy, childhood absence epilepsy, preventing post-traumatic epilepsy, and hormone therapy. The Institute is working with the community on developing a major follow up conference "Curing Epilepsy II" for 2007 that will continue the interaction catalyzed by the Benchmarks process.

Muscular dystrophy: In accordance with the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84), the Muscular Dystrophy Coordinating Committee (MDCC) developed an NIH research and education plan for the muscular dystrophies. The broad goals of this plan served as the framework for an MDCC Scientific Working Group which met in August 2005 to develop a detailed action plan for muscular dystrophy research. The NINDS, the National Institute of Child Health and Human Development (NICHD), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) jointly fund a network of six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, which play a central role in the implementation efforts. The NIH has recently supplemented the Centers to improve training and to support scientific conferences on specific topics. Among other efforts, grant solicitations focus on critical issues in understanding the muscular dystrophies and on enhancing translational research to develop therapies.

Minority Health and Health Disparities: Led by the NINDS Office of Minority Health and Research (OMHR), the Institute encourages the training and development of minority research and health professionals and conducts research to address health disparities. The OMHR led the development of the NINDS Five-Year Strategic Plan on Minority Health Disparities, with a focus on stroke, HIV associated neurological disease, neurological complications of diabetes, chronic pain, epilepsy, and children's health issues. The continuing Specialized Neuroscience

Research Programs (SNRPs) are an important component of the OMHR programs. The eight SNRPs strengthen the research capabilities of basic and clinical neuroscience research programs at minority institutions. The NINDS also leads the NIH in pursuing a Government Performance and Results Act (GPRA) goal to identify culturally appropriate, effective stroke prevention programs for nation-wide implementation in minority communities by FY 2010. The Institute supports many relevant clinical studies, clinical trials, and epidemiological investigations. Among these, the NINDS is an active participant in the DHHS Stroke Belt Elimination Initiative (SBEI) through the REGARDS study (Reasons for Geographic and Racial Differences in Stroke). By 2005 REGARDS had enrolled more than 20,000 people in a study to determine stroke risk in a national sample of white and African-American subjects.

Counterterrorism: Many chemical agents and toxins affect the nervous system and could serve as terrorist weapons. The nervous system is also vulnerable to infectious agents that could be used in a terrorist attack. The NINDS works with the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), other parts of the NIH, the DHHS leadership, and other government agencies to plan overall research strategies and identify high priority counterterrorism research issues that the NINDS is best qualified to address. Persistent seizures, neuroprotection, and neurodegeneration are among these concerns, as is the greater diversity of the general public compared to the military in age and health status. In 2003, the NINDS initiated a program that supplements current grantees to expand ongoing research to issues relevant to counterterrorism. In April 2004, the NINDS organized a scientific workshop that brought together experts in military research programs with scientists from the academic neuroscience community to help define priorities, with a follow up meeting in February 2005 that focused specifically on seizures resulting from chemical agent exposure. In 2005, the Institute issued requests for information on potential contract resources for developing medical countermeasures. The Institute will continue to pursue research on neurological counterterrorism issues as appropriate within the context of the overall NIH, DHHS and government-wide counterterrorism planning efforts.

Training: Training basic and clinical neuroscientists is essential to the NINDS mission. The Institute supports most trainees as scientists working on research grants to established investigators. Pre- and postdoctoral students are also supported through individual and institutional training awards, and basic and clinical scientists compete for early and mid-career development awards, including programs to encourage minority participation. The NINDS has placed increased emphasis on recruiting and training physician-scientists, supporting their career development and improving mentoring for these researchers. The NINDS Intramural program offers opportunities for talented high-school, undergraduate, graduate and medical students, as well as more advanced training. The NINDS participates in the NIH Loan Repayment Program, which encourages health professionals to undertake clinical and pediatric research. Through the NIH Neuroscience Blueprint, the Institute supports training of basic scientists in the neurobiology of disease. NIH Roadmap training programs are also relevant to the NINDS mission, including training in neurodevelopmental toxicology, neurobehavioral development, autism, regenerative medicine, computational neurosciences, and neuroengineering.

International Programs: Health a global issue and research is increasingly a worldwide enterprise. In 2004, the NINDS created the Office of International Activities to promote

international research, training, and collaborations that are relevant to the Institute's mission. These international activities provide access to unique resources and expertise. Discovery of genes for Parkinson's, ALS, peripheral neuropathies, and other neurological diseases, for example, has relied heavily on international efforts. Recent NINDS international activities include: an Australian researcher who developed a proof of concept for a new muscular dystrophy therapy that has now moved to a clinical trial; a visiting scientist who received training in the NINDS intramural program and has returned to Argentina to develop, with NINDS support, a new therapy to stimulate stroke recovery; and a new study that capitalizes on unique resources in Norway that permit an unprecedented view of the longitudinal development of autism spectrum disorders and the role of gene-environment interactions. In the coming year, the NINDS Office of International Activities will continue to work closely with the NIH Fogarty International Center on programs focused on brain disorders, bioethics, cooperative research, and training. The Office also continues to lead other NINDS efforts to foster collaboration among international neuroscientists, including the US-Japan Brain Research Cooperation Program.

Public Information: The NINDS, through its Office of Communications and Public Liaison, is a source of reliable information about neurological disorders for the public, the press, and professional organizations. Each year the Institute responds to thousands of requests for information by phone, email, or letter, and provides fact sheets about hundreds of neurological disorders, news in neuroscience, and descriptions of NINDS activities, including funding opportunities, on its heavily used website (http://www.ninds.nih.gov/). The site also provides links to helpful resources including non-governmental organizations relevant to particular diseases, information for people seeking to participate in clinical trials, and the wealth of health information provided by the National Library of Medicine. A major continuing effort is underway to provide information in Spanish as well as English.

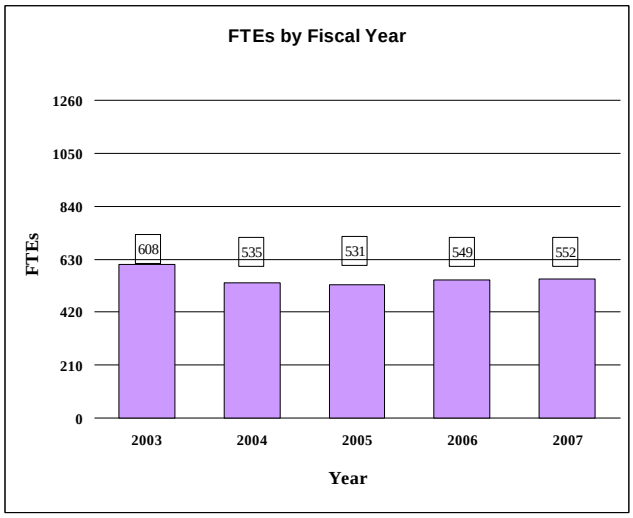
The Office also serves as the point of contact for more than 300 non-governmental organizations whose focus is within the mission of the NINDS. In June of 2005, the Institute brought together approximately 100 people, including 75 representatives of non-profit organizations, at the NIH Lister Hill Center in Bethesda, Maryland for a day of presentations, informal interaction, and group discussions designed for them by the Institute. Based on the strong positive feedback from participants, the NINDS will hold similar meetings in the future.

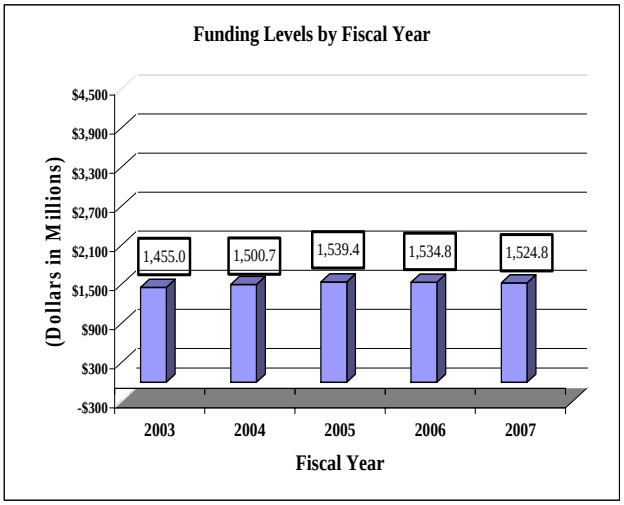
Since the middle of the 1990s, the NINDS has taken an especially active role in promoting understanding of the serious public health issues related to stroke, through billboards, public service radio and television advertising, a community education kit with a consumer education video, posters, brochures in both English and Spanish, strategic partnerships with interested organizations, media outreach, faith-based media events, a traveling exhibit, and online public service marketing. The campaign has included professional education and minority outreach, including a training DVD in partnership with the American Stroke Association, the American Academy of Neurology, and the National Stroke Association, and a joint initiative with the U.S. Centers for Disease Control and Prevention (CDC) through their state health programs. Among the significant recent efforts are a stroke awareness video for Hispanics and addition of stroke information for seniors to the NIHSeniorHeath web site. The NINDS also chairs the Brain Attack Coalition which brings together professional, voluntary and government organizations with a common mission of reducing the occurrence, disabilities and death associated with stroke.

Budget Policy

The Fiscal Year 2007 budget request for the National Institute of Neurological Disorders and Stroke (NINDS) is $1,524,750,000, a decrease of $10,007,000 and -0.7 percent from the FY 2006 Appropriation. Included in the FY 2007 request is NINDS's support for the trans-NIH Roadmap initiatives, estimated at 1.2% of the FY 2007 budget request. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NINDS are shown in the graphs below. Note that as the result of several administrative restructurings in recent years, FTE data is non-comparable.





NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. We estimate that the average cost of competing RPGs will be $390,000 in FY 2007. While no inflationary increases are provided for direct recurring costs in noncompeting RPGs, where the NINDS has committed to a programmatic increase for an award, such increases will be provided.

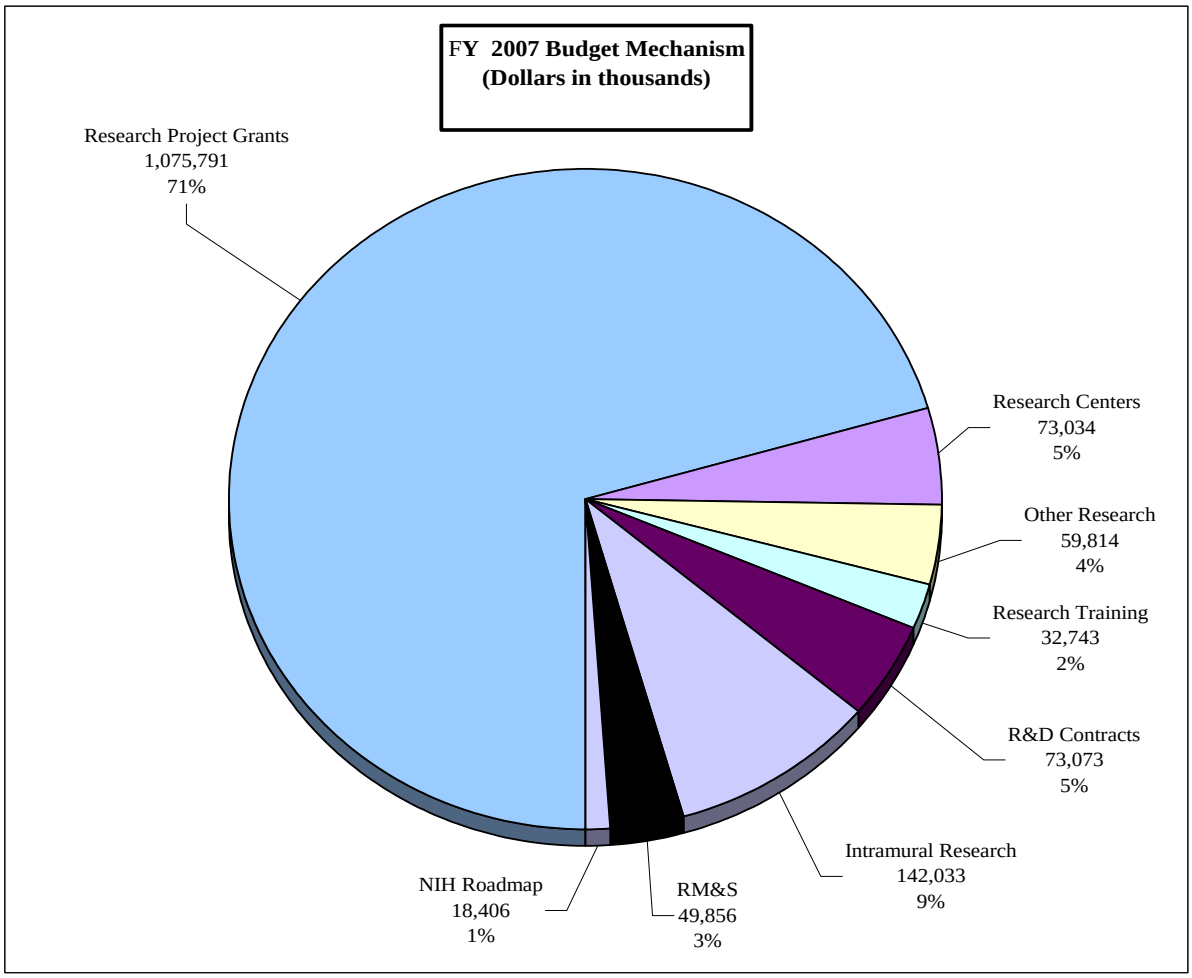
NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NINDS, $1,080,000 will be used to support 12 awards for the new K/R "Pathway to Independence" program.

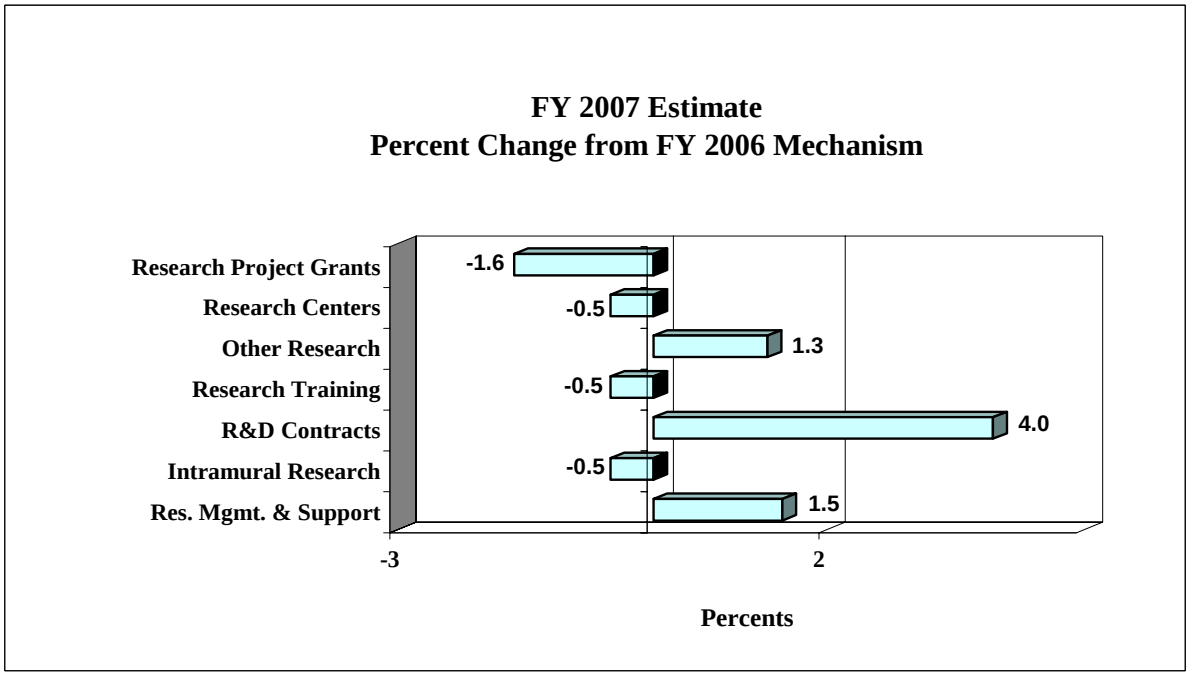
NINDS will also support the Genes, Environment, and Health Initiative (GEHI) to: 1) accelerate discovery of the major genetic factors associated with diseases that have a substantial public health impact; and 2) accelerate the development of innovative technologies and tools to measure dietary intake, physical activity, and environmental exposures, and to determine an individual's biological response to those influences. The FY 2007 request includes $2,557,000 to support this project.

In the FY 2007 request, stipend levels for trainees supported through the Ruth L. Kirschstein National Research Service Awards will remain at the FY 2006 levels.

The FY 2007 request includes funding for 62 research centers, 366 other research grants, including 276 career awards, and 155 R&D contracts. Intramural Research decreases by 0.5 percent. Research Management and Support increases by 1.5 percent.

The mechanism distribution by dollars and percent change are displayed below:





NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Mechanism - Total

MECHANISM	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	1,997	$790,297,000	2,083	$842,999,000	1,920	$809,391,000
Administrative supplements	(148)	7,341,000	(197)	11,810,000	(196)	11,751,000
Competing:						0
Renewal	263	117,634,000	195	87,217,000	211	94,186,000
New	434	155,005,000	322	114,925,000	348	124,109,000
Supplements	3	576,000	2	427,000	2	461,000
Subtotal, competing	700	273,215,000	519	202,569,000	561	218,756,000
Subtotal, RPGs	2,697	1,070,853,000	2,602	1,057,378,000	2,481	1,039,898,000
SBIR/STTR	109	37,157,000	106	36,167,000	105	35,893,000
Subtotal, RPGs	2,806	1,108,010,000	2,708	1,093,545,000	2,586	1,075,791,000
Research Centers:						
Specialized/comprehensive	61	74,546,000	62	73,401,000	62	73,034,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	61	74,546,000	62	73,401,000	62	73,034,000
Other Research:						
Research careers	271	43,345,000	271	43,029,000	276	43,894,000
Cancer education	0	0	0	0		0
Cooperative clinical research	26	2,337,000	27	2,311,000	27	2,299,000
Biomedical research support	0	0	0	0		0
Minority biomedical research support	5	1,576,000	5	1,561,000	5	1,553,000
Other	62	12,783,000	58	12,129,000	58	12,068,000
Subtotal, Other Research	364	60,041,000	361	59,030,000	366	59,814,000
Total Research Grants	3,231	1,242,597,000	3,131	1,225,976,000	3,014	1,208,639,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	376	14,250,000	368	14,249,000	364	14,178,000
Institutional awards	381	18,658,000	379	18,658,000	379	18,565,000
Total, Training	757	32,908,000	747	32,907,000	743	32,743,000
Research & development contracts	146	71,075,000	149	70,293,000	155	73,073,000
(SBIR/STTR)	(1)	(83,000)	(2)	(500,000)	(2)	(510,000)
	FTEs		FTEs		FTEs	
Intramural research	385	134,617,000	393	142,747,000	396	142,033,000
Research management and support	146	48,519,000	155	49,119,000	155	49,856,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
NIH Roadmap for Medical Research	0	9,732,000	1	13,715,000	1	18,406,000
Total, NINDS	531	1,539,448,000	549	1,534,757,000	552	1,524,750,000
(Clinical Trials)		(132,543,000)		(131,791,000)		(130,473,000)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research		$1,346,580		$1,329,176		$1,314,455		($14,721)
Intramural research	385	134,617	393	142,747	396	142,033	3	(714)
Res. management & support	146	48,519	155	49,119	155	49,856	0	737
NIH Roadmap for Medical Research	0	9,732	1	13,715	1	18,406	0	4,691
Total	531	1,539,448	549	1,534,757	552	1,524,750	3	(10,007)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Summary of Changes

FY 2006 Estimate				$1,534,757,000
FY 2007 Estimated Budget Authority				1,524,750,000
Net change				(10,007,000)
	FY 2006 Appropriation		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$49,012,000		$706,000
b. Annualization of January 2006 pay increase		49,012,000		380,000
c. January 2007 pay increase		49,012,000		809,000
d. Payment for centrally furnished services		34,797,000		522,000
e. Increased cost of laboratory supplies, materials, and other expenses		58,938,000		1,168,000
Subtotal				3,585,000
2. Research Management and Support:				
a. Within grade increase		19,062,000		328,000
b. Annualization of January 2006 pay increase		19,062,000		148,000
c. January 2007 pay increase		19,062,000		315,000
d. Payment for centrally furnished services		12,723,000		191,000
e. Increased cost of laboratory supplies, materials, and other expenses		17,334,000		323,000
Subtotal				1,305,000
Subtotal, Built-in				4,890,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Summary of Changes--continued

CHANGES	2006 Current Appropriation		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,083	$854,809,000	(163)	($33,667,000)
b. Competing	519	202,569,000	42	16,187,000
c. SBIR/STTR	106	36,167,000	(1)	(274,000)
Total	2,708	1,093,545,000	(122)	(17,754,000)
2. Research centers	62	73,401,000	0	(367,000)
3. Other research	361	59,030,000	5	784,000
4. Research training	747	32,907,000	(4)	(164,000)
5. Research and development contracts	149	70,293,000	155	2,780,000
Subtotal, extramural				(14,721,000)
	FTEs		FTEs	
6. Intramural research	393	142,747,000	3	(4,299,000)
7. Research management and support	155	49,119,000	0	(568,000)
8. Cancer control and prevention	0	0	0	0
9. Construction		0		0
10. Buildings and Facilities		0		0
11. NIH Roadmap for Medical Research	1	13,715,000	0	4,691,000
Subtotal, program		1,534,757,000		(14,897,000)
Total changes	549		3	(10,007,000)

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Budget Authority by Object

	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	549	552	3
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	$152,153	$155,972	$3,819
Average GM/GS grade	11.7	11.8	0.1
Average GM/GS salary	$81,294	$83,334	$2,040
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$86,082	$88,243	$2,161
Average salary of ungraded positions	105,685	108,338	2,653

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$26,481,000	$27,260,000	$779,000
11.3 Other than Full-Time Permanent	20,160,000	20,811,000	651,000
11.5 Other Personnel Compensation	1,225,000	1,262,000	37,000
11.7 Military Personnel	695,000	718,000	23,000
11.8 Special Personnel Services Payments	6,297,000	6,612,000	315,000
Total, Personnel Compensation	54,858,000	56,663,000	1,805,000
12.0 Personnel Benefits	12,727,000	13,119,000	392,000
12.2 Military Personnel Benefits	489,000	505,000	16,000
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	**68,074,000**	**70,287,000**	**2,213,000**
21.0 Travel & Transportation of Persons	3,444,000	3,385,000	(59,000)
22.0 Transportation of Things	310,000	305,000	(5,000)
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	57,000	58,000	1,000
23.3 Communications, Utilities & Miscellaneous Charges	907,000	903,000	(4,000)
24.0 Printing & Reproduction	700,000	707,000	7,000
25.1 Consulting Services	1,800,000	1,777,000	(23,000)
25.2 Other Services	10,249,000	10,073,000	(176,000)
25.3 Purchase of Goods & Services from Government Accounts	114,126,000	113,132,000	(994,000)
25.4 Operation & Maintenance of Facilities	6,230,000	6,068,000	(162,000)
25.5 Research & Development Contracts	28,517,000	31,074,000	2,557,000
25.6 Medical Care	487,000	474,000	(13,000)
25.7 Operation & Maintenance of Equipment	8,800,000	8,713,000	(87,000)
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**170,209,000**	**171,311,000**	**1,102,000**
26.0 Supplies & Materials	9,717,000	9,471,000	(246,000)
31.0 Equipment	8,738,000	8,532,000	(206,000)
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	1,258,883,000	1,241,382,000	(17,501,000)
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	3,000	3,000	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**1,452,968,000**	**1,436,057,000**	**(16,911,000)**
NIH Roadmap for Medical Research	**13,715,000**	**18,406,000**	**4,691,000**
Total Budget Authority by Object	**1,534,757,000**	**1,524,750,000**	**(10,007,000)**

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Salaries and Expenses

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$26,481,000	$27,260,000	$779,000
Other Than Full-Time Permanent (11.3)	20,160,000	20,811,000	651,000
Other Personnel Compensation (11.5)	1,225,000	1,262,000	37,000
Military Personnel (11.7)	695,000	718,000	23,000
Special Personnel Services Payments (11.8)	6,297,000	6,612,000	315,000
Total Personnel Compensation (11.9)	**54,858,000**	**56,663,000**	**1,805,000**
Civilian Personnel Benefits (12.1)	12,727,000	13,119,000	392,000
Military Personnel Benefits (12.2)	489,000	505,000	
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**68,074,000**	**70,287,000**	**2,213,000**
Travel (21.0)	3,444,000	3,385,000	(59,000)
Transportation of Things (22.0)	310,000	305,000	(5,000)
Rental Payments to Others (23.2)	57,000	58,000	1,000
Communications, Utilities and Miscellaneous Charges (23.3)	907,000	903,000	(4,000)
Printing and Reproduction (24.0)	700,000	707,000	7,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	1,261,000	1,238,000	(23,000)
Other Services (25.2)	10,249,000	10,073,000	(176,000)
Purchases from Govt. Accounts (25.3)	65,920,000	64,083,000	(1,837,000)
Operation & Maintenance of Facilities (25.4)	6,230,000	6,068,000	(162,000)
Operation & Maintenance of Equipment (25.7)	8,800,000	8,713,000	(87,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**92,460,000**	**90,175,000**	**(2,285,000)**
Supplies and Materials (26.0)	9,592,000	9,349,000	(243,000)
Subtotal, Non-Pay Costs	107,470,000	104,882,000	(2,588,000)
Total, Administrative Costs	**175,544,000**	**175,169,000**	**(375,000)**

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

FY 2006 House Appropriations Committee Report Language (H. Rpt. 109-143)

Item

Stroke – The Committee continues to place a high priority on stroke research and encourages NINDS to allocate resources to basic, clinical and translational research into stroke, which is a major contributor to late-life dementia and a leading cause of permanent disability. The Committee encourages NINDS to continue implementing the long-range strategic plan for stroke research and to continue searching for novel approaches to improve stroke diagnosis, treatment, rehabilitation and prevention. (p.71)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) continues to implement the goals of the Stroke Progress Review Group report across its stroke research portfolio. In addition to a vigorous program of 60 clinical trials in stroke, NINDS continues to expand the capabilities of its Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS), a national network of centers that conducts translational research and early phase clinical projects; shares data; and promotes new approaches to stroke therapies. NINDS now supports six SPOTRIAS sites, and is providing these centers with supplements to support cooperative programs in blood collection for protein and genetic analyses. These analyses are essential for the study of stroke genes and the development of stroke biomarkers (biological markers of disease severity, progression, or response to treatment). Recent SPOTRIAS milestones include the development of a common clinical database; enrollment of more than 350 individuals into treatment protocols; the initiation of two collaborative clinical trials; and the training of 24 research fellows. NINDS hopes to expand the program further, and has re-issued its Program Announcement (PA) recruiting SPOTRIAS applications in April 2005.

NINDS is also addressing several other major issues in neurovascular disease, including stroke, through targeted grant solicitations and other program activities. NINDS has made a total of 14 stroke-related awards since the start of FY 2005 under two recent PAs on "Neurovascular Mechanisms of Brain Function and Disease" and "Neuroprotective CNS Barriers in Neurological Diseases," which were jointly sponsored by NINDS and several other Institutes at the National Institutes of Health. NINDS has also sponsored a workshop to develop diagnostic criteria for vascular cognitive impairment (VCI; a disorder of cognitive dysfunction caused by vascular disease in the brain), and has received a number of applications in response to a related PA, focused on the "Genetics and Pathobiology of VCI." The links between cerebrovascular disease and cognitive impairment are increasingly appreciated among researchers, and NINDS hopes to

accelerate this research with its PA. The NINDS also joined the National Heart, Lung, and Blood Institute (NHLBI) in July 2004 on a Request for Applications (RFA) entitled "Novel Targets and Therapy Development for Ischemic Stroke," which was designed to stimulate development of new therapeutic agents or approaches for cerebral ischemia. In addition to these efforts, NINDS is exploring immune strategies as a potentially effective means of preventing and treating stroke, and in March 2005, the Institute co-sponsored a workshop on "Immuno-modulation Strategies for Preventing Vascular Disease of the Brain and Heart," with the Canadian Stroke Network and NHLBI. Lastly, NINDS is eager to aid the translation of promising therapies for stroke into clinical testing, and announced in August 2005 that it is offering administrative supplements for the development of stroke preclinical trials consortia.

NINDS also continues to encourage deposits from stroke researchers into its DNA and cell line repository. This facility, currently housed at the Coriell Cell Repositories in New Jersey, now contains nearly 2500 samples from individuals affected by stroke, and more than 1500 control samples. NINDS-funded researchers have already published several scientific papers on stroke based on data collected from repository samples.

Item

Epilepsy - Epilepsy remains a major, unsolved public health problem affecting the lives of millions of Americans and their families. The Committee seeks intensified efforts by the Institute to produce breakthroughs in the prevention, treatment, and eventual cure of epilepsy. The Committee applauds the development of benchmarks for epilepsy research resulting from the ''Curing Epilepsy: Focus on the Future'' conference held in 2000 and encourages NINDS to address important research issues raised at the ''Living Well with Epilepsy II'' conference held in 2003. The Committee encourages NINDS to continue to allocate resources to the anti-epileptic drug development program, and to report to the Committee in next year's hearings on its activities to further these important areas of research. (p. 71)

Action taken or to be taken

The NINDS continues to implement the "Benchmarks for Epilepsy Research," a strategy developed with the professional and patient voluntary communities to measure progress toward a cure for epilepsy. For example, the NINDS sponsors a wealth of basic and translational research studies on the concept of epileptogenesis, the process by which the "normal" brain becomes hyperexcitable after an insult or injury, leading to spontaneous, recurrent seizures (Benchmarks Area I.) Among its clinical epilepsy projects, the Institute is funding a pilot clinical trial of a new generation anti-epileptic drug, levetiracetam, to test its safety in individuals with increased risk of epilepsy caused by traumatic brain injury. This study is directly relevant to Benchmarks Area II- prevention of seizures in those at risk. The focus of Benchmarks Area III is on developing therapies without side effects that will eliminate seizures in those with epilepsy. Along with a diverse range of extramural studies supported by the NINDS, the Institute's Anticonvulsant Screening Program (ASP), is particularly focused on accelerating progress in this area of the Epilepsy Benchmarks. The ASP, formerly known as the Antiepileptic Drug Development Program, is a drug discovery program to conduct evaluations of the potential efficacy and toxicity of candidate compounds in validated epilepsy model systems. As a result

of its hundreds of public-private partnerships with investigators in academia, the pharmaceutical and biotechnology industries, the ASP has aided the development of eight marketed drugs and seven new compounds currently undergoing clinical evaluation. The ASP also leads the Institute's major effort to develop improved animal models of epilepsy. Over the next five years, the ASP will focus on developing novel agents for intractable forms of epilepsy and finding agents that prevent the development of epilepsy in those at risk for the disease.

The "Living Well with Epilepsy II" conference, supported by the Centers for Disease Control and Prevention (CDC), identified priority areas for public health and quality of epilepsy care. The NINDS epilepsy research portfolio also includes studies that are relevant to Living Well priorities in the area of early recognition, diagnosis and treatment and in the area of stigma and quality of life of people with epilepsy. The components of the NIH and CDC that support epilepsy related research coordinate their efforts at regular meetings of an Interagency Epilepsy Working Group.

The NINDS intends to build on the progress made in the Epilepsy Benchmarks, the Living Well priorities, and other areas of epilepsy research by continuing its focused effort to support career development and training for young investigators and by supporting scientific meetings on several critical topics. In May 2005, the NINDS, the National Institute of Mental Health (NIMH), and the American Epilepsy Society jointly sponsored an international workshop on treatment of nonepileptic seizures (NES), a neuropsychiatric seizure disorder that crosses traditional boundaries between neurology and psychology/psychiatry. As a result of this meeting, the NIMH and the NINDS issued a request for applications on "Collaborative Research on Mental and Neurological Disorders." In 2006 the NINDS will host a workshop on "Models of Geriatric Epilepsy," the fourth in a series of workshops to develop improved animal models of epilepsy. Another meeting planned for 2006 will focus on "Identifying Biomarkers of Epileptogenesis" in those at risk for epilepsy, a topic relevant to the epilepsy prevention goal in Benchmarks Area II. Lastly, to formally initiate the next phase of planning and priority setting in epilepsy research, the NINDS and partnering organizations will sponsor a second large, broad-based meeting of the epilepsy community, the "Curing Epilepsy II" conference, in March 2007.

Item

Alzheimer's Disease – NINDS is currently supporting both preclinical and translational research intended to expand the pool of therapeutic agents for treating Alzheimer's disease. For example, a recent NINDS-supported study tested a drug that interferes at a specific point in the cholesterol pathway that contributes to the generation of amyloid protein, a hallmark of Alzheimer's. The study resulted in a 99 percent reduction in brain amyloid in a mouse model of the disease, suggesting that this may provide a novel approach for developing a therapeutic intervention for Alzheimer's disease. The Committee encourages NINDS to continue to assign a high priority to Alzheimer research, and to work closely with NIA, NIMH and other institutes. (p. 71)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) continues to explore a number of therapeutic targets for Alzheimer's disease (AD) at the preclinical level. One

promising target is tau, a protein in the skeleton of neurons that can accumulate abnormally and contribute to the degeneration of neurons in AD. To try to reduce the impact of abnormal tau, a group of investigators funded by the National Institute on Aging (NIA), NINDS, and the Alzheimer's Association tested lithium, a drug used for many years to treat bipolar disorder in humans. In this study, lithium was found to effectively reduce abnormal modifications of tau in mice that were genetically engineered to overexpress a human version of mutant tau protein. Moreover, the lithium could also reduce neuronal degeneration if administered before significant structural abnormalities occurred in affected neurons.

A second potential target is a growth factor receptor called p75NTR, which was originally believed to mediate the toxic effects of amyloid-beta protein on neurons. In a recent study, NINDS-funded researchers found that instead of mediating toxic effects, p75NTR may actually serve a protective function, even in the presence of levels of amyloid 2500 times higher than those found in the spinal fluid of people with AD.

Nicastrin, a molecule believed to be involved in the buildup of abnormal amyloid in the cell, is a third potential therapeutic target for AD therapeutics development. Another NINDS-funded study has demonstrated that nicastrin is required not only for the release of amyloid beta into the spaces between cells, but that it also plays a role in "clipping out" toxic amyloid-beta from a longer precursor molecule. NINDS-funded investigators will continue to explore these and other cellular targets, until they can identify the targets that are most suitable for translational development and clinical trials.

NINDS also continues to participate in regular meetings of the trans-NIH Alzheimer's Disease Coordinating Committee, which includes NIA and several other NIH Institutes and Centers. At its most recent meeting, the Committee discussed expansion of the group to include additional NIH Institutes and Centers, the relevance of the Committee's activities to other neurodegenerative diseases, and the development of a more organized format for exchanging information among Committee members. As just one example of the type of collaborations the Committee facilitates, NINDS staff has worked with the NIA to identify appropriate participants for two NIA meetings on AD: a small planning meeting held in December 2005, and a larger conference scheduled for 2006.

Item

Parkinson's Disease – The Committee supports the innovative multidisciplinary research and training concerning Parkinson's disease provided by the Morris K. Udall Parkinson's Disease Research Centers of Excellence. The additional research opportunities and discoveries made by Udall Center scientists are leading to improved diagnosis and treatment of patients with Parkinson's. The Committee commends both the basic and clinical objectives of the Centers that, together, enhance research effectiveness in a multidisciplinary setting.

The Committee commends NINDS for participating in a community- wide examination of private and pubic Parkinson's disease research funding through the Parkinson's Community Research Advisory Council. The Committee recommends that NINDS continues to participate in this effort.

The Committee commends the Director for participating in the Neuroscience Blueprint, which create new opportunities for collaborative research across institutes and through public-private partnerships. Specifically, the Committee encourages collaborations with other institutes in the areas of genetics, cell biology, pathology/ epidemiology, non-human models, biomarkers, neuroimaging, gene therapy, surgical approaches, drug development, cell replacement therapy (i.e., stem cells), and mental health. (p. 72)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) continues its productive collaborations with the other Institutes and Centers across the National Institutes of Health (NIH) to accelerate research in Parkinson's disease (PD). For example, NINDS worked jointly with the National Institute of Mental Health (NIMH) to plan a November 2005 workshop on psychosis and PD; supported a Request for Applications in September 2004 on "Collaborative Studies on Alzheimer and Related Diseases" with the National Institute on Aging (NIA); coordinated the planning of the annual neural prosthesis/deep brain stimulation workshop with the NIA and the National Institute of Biomedical Imaging and Bioengineering; and joined the NIA in supporting a workshop entitled "Clinico-Pathological Correlations in the Lewy Body Dementias" in September 2004. In addition, NINDS and NIA are working together as each Institute improves its data collection systems for use with its PD and Alzheimer's disease research centers. Along these lines, the National Institute of Environmental Health Sciences is establishing guidelines for a minimum set of epidemiological data that can be used by the NINDS-funded PD Data Organizing Center, which will serve as a centralized data repository for the Morris K. Centers for Excellence in Parkinson's Disease Research Centers, as well as other NIH-funded and private PD research centers. To strengthen this collaborative spirit further, the NINDS continues to hold regular meetings of the PD Coordinating Committee, which includes representatives of 12 NIH Institutes and Centers, as well as representatives from the Department of Veterans Affairs and the Department of Defense.

Another collaborative effort, the Neuroscience Blueprint, involves multiple Institutes at the NIH, including the NINDS, the NIA, and the NIMH, among others. It was designed to complement disease-focused programs (such as those focused on PD) at NINDS and these other Institutes, and will provide tools, resources, and training for the neuroscience research community. Initiatives for FY 2005 included the development of graduate level courses on the neurobiology of disease and expansion of efforts to map and characterize gene expression in the nervous system. The Neuroscience Blueprint has already released FY 2006 Requests for Applications to develop new neuroimaging strategies and core research facilities. Initiatives under development include training in neuroimaging; the creation of mouse genetic models; and the development of a clinical tool to assess neurological, behavioral, and mental health.

Lastly, the Parkinson's Community Research Advisory Council (PC-RAC) is currently undertaking a community-wide examination of private and public PD research funding. While NINDS has provided the PC-RAC with information on its funding activities, NINDS conducts its own annual analysis of the international PD research portfolio based on the topics identified in the PD Research Agenda. NINDS believes that it can be useful to analyze funded grants from

many different perspectives, and the Institute will continue to cooperate with the private funding community by providing any data needed for their efforts in this area.

Item

Transmissible spongiform encephalopathies (TSE) - The Committee recognizes the efforts of NINDS, in collaboration with NHLBI, to fund contracts for the development of a biological assay for TSE. The Committee requests that the Director of the Institute be prepared to report on the progress made toward the development of a TSE bioassay at the fiscal year 2007 appropriations hearing. The Committee is particularly interested in the success in detecting disease-causing agents in blood, saliva, cerebrospinal fluid, and other bodily fluids, as well as lymphoid tissue, especially tonsils. (p. 72)

Action taken of to be taken

The NINDS, and NIH generally, are continuing the long history of support for research on TSEs. This year NIH scientists made significant advances in understanding how these diseases are transmitted and harm the brain, and in applying those insights to diagnose TSEs and detect them in various tissues. Because of the unusual nature of prion diseases, the usual approaches to amplifying and detecting bacteria and viruses to diagnose disease and detect blood contamination do not work for TSEs. According to the prevailing theory, a misshaped form of a normal protein, called a prion, causes other normally folded prion proteins to take on the abnormal form, which leads to destruction of brain tissue and the devastating symptoms of the disease. This year NIH funded scientists made substantial progress toward the very challenging goal of developing practical tests for the very low levels of prion infectivity in blood and other non-brain tissues. One research team, for example, devised a method to amplify the low level of prions in blood by more than 10 million fold. The technique builds on the basic understanding of how abnormal prion proteins coax other prions to take on the abnormal shape. After amplification, conventional protein detection methods can be applied. When tested on blood from hamsters experimentally infected with a form of TSE, the procedure had 89% sensitivity, detecting abnormal prions in blood from 16 of 18 infected animals, and was 100% specific, showing no errors in uninfected samples. Work is underway to apply this method to other animals and to humans. In addition to improving the safety of the blood supply and surveillance of cattle, a more sensitive TSE test is important for developing therapies, which are more likely to work the earlier in the disease process they can be administered.

Item

Peripheral Neuropathy - As many as 20 million Americans suffer from peripheral neuropathy, a neurological disorder that causes debilitating pain, weakness in the arms and legs, and difficulty walking. Peripheral neuropathy affects approximately one-third of diabetics, or about 5.1 million people, while other forms of neuropathy are inherited; associated with cancer, kidney disease, or infections like hepatitis, HIV/AIDS, or Lyme disease; or caused by autoimmunity, traumatic injuries, poor nutrition, toxins, and certain medications. While significant research is underway on diabetic neuropathy and HIV/AIDS-related neuropathy, the Committee encourages NINDS to strengthen its research portfolio on other forms of neuropathy. The Committee is

pleased to learn that NINDS plans to convene a workshop with distinguished scientists to identify research goals aimed at expanding the research knowledge base and identifying potential therapies. (p. 72)

Action taken or to be taken

Peripheral neuropathy is a common neurological condition that is associated with a number of diseases. The National Institute of Neurological Disorders and Stroke (NINDS) funds a wide range of research on the peripheral neuropathies including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, Charcot-Marie Tooth disorder (CMT), toxic chemical/drug-induced neuropathies, inflammatory neuropathies, and neuropathic pain.

Studies currently funded by NINDS focus on understanding the underlying genetic basis, molecular and cellular mechanisms, and natural history of these disorders. In addition, NINDS-funded researchers are working to identify and develop potential therapies to treat these disorders. Researchers in the NINDS intramural program also focus on inherited and acquired neuropathies.

The NINDS research portfolio includes many studies on basic physiological processes that underlie some of these peripheral neuropathies. Some forms of CMT are associated with disruptions in the myelin sheath, a covering of protein and fatty substances that insulates nerve fibers and prevents dissipation of the electrical signals. The NINDS supports a wide range of studies examining the process of myelination and its regulation, as well as the protein components that make up the myelin sheath. Since many of the genes that cause CMT are also essential to axon and myelin development, an understanding of the regulation of nerve development is essential to progress in understanding and treating these disorders. In addition, many forms of neuropathy cause significant pain, and NINDS funds studies investigating the cellular and molecular basis of neuropathic pain and developing potential treatments to alleviate the pain.

The NINDS is planning a workshop for Spring 2006 on the peripheral neuropathies, including inherited, infectious, and inflammatory neuropathies. NINDS-funded researchers working in this area, as well as those from other Institutes at the NIH with an interest in the peripheral neuropathies, will be invited to participate. The purpose of the workshop is to identify and discuss research opportunities, needs, and gaps in our knowledge of the peripheral neuropathies in order to both improve our understanding of and develop potential therapies for these disorders. Because disease mechanisms may be shared among multiple types of neuropathies, this is an important time to bring together investigators working on diverse neuropathies. Rather than focus on each form of neuropathy as a separate entity, the workshop will strive to integrate researchers working on the different forms of peripheral neuropathy to discuss topics such as the molecular and cellular basis of disease, diagnostic tools, treatment strategies, the natural history of the disorders, and clinical trial endpoint measures. This approach has proven to be a very successful format in previous workshops sponsored by NINDS, fostering collaborative discussions among researchers from different areas, giving them an opportunity to approach questions about their specific research from a different perspective, and identifying commonalities among the different disorders.

Item

Juvenile diabetic neuropathy -- The Committee commends NINDS for its recognition of diabetic neuropathy as a serious problem of juvenile diabetes. The Committee encourages the Institute to work with other agencies on the development of new animal models of diabetic neuropathies to aid in the development and testing of novel clinical treatments for diabetic peripheral and autonomic neuropathies. (p. 72)

Action taken or to be taken

Peripheral sensory neuropathy is a common neurological condition which is associated with type 1 ("juvenile") and type 2 diabetes as well as other disorders. The National Institute of Neurological Disorders and Stroke (NINDS) supports studies on understanding the etiology of diabetic neuropathy, including the possibility that glucose-mediated nerve cell death results in neuropathy, as well as research on potential therapeutic targets, such as growth factors. NINDS also funds a large-scale, cross-sectional clinical and epidemiological study of neuropathic complications in diabetic patient populations as well as a natural history study to examine small-nerve fiber function and to follow the progression of diabetes-related dysfunction in patients over a period of at least three years. These natural history studies are important in helping to define the best measures of function and quality of life for subsequent use in clinical trials.

NINDS-funded researchers are pursuing a variety of options for therapeutic development in diabetic neuropathy, including improved glycemic control, gene therapy, and use of growth factors (e.g., glial cell-derived neurotrophic factor or GDNF) to prevent axonal degeneration. In addition, NINDS has a strong basic science portfolio in axon and myelin development, structure, and function. These studies are essential to providing the basis for future therapeutic development in all of the peripheral neuropathies.

Over the past few years, NINDS, in collaboration with other institutes, has issued a number of initiatives to stimulate research in diabetic neuropathy. Of particular relevance, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in partnership with NINDS and the National Heart, Lung, and Blood Institute (NHLBI), released a request for applications (RFA) in August 2005 for an "Animal Models of Diabetic Complications Consortium." The intent of this RFA is to assemble a cross-disciplinary group of investigators to form Pathobiology sites that will support the Animal Models of Diabetic Complications Consortium (AMDCC). The AMDCC was established in 2001 to generate new animal models to study the pathology of diabetes complications with the aim of understanding the underlying cause, prevention and treatment of the disease. The animal models generated by the AMDCC are being used to elucidate the role of specific genes or chromosomal regions in the pathogenesis of these complications. The AMDCC Pathobiology sites will (1) propose new mouse models to be developed by the Consortium that will replicate one or more diabetic complications, and (2) discover and characterize the basic pathophysiologic mechanisms underlying disease in these and other models of complications. A number of diabetic complications involving different organ systems and biochemical pathways are cited in the RFA, and include diabetic

complications of the nervous system such as neuropathy. NINDS staff are active participants in the AMDCC, participating in initiatives and meetings of the consortium.

In addition, NIDDK, along with five other institutes, including NINDS, recently released another request for applications, "Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) to Develop New Therapeutics and Monitoring Technologies for Type 1 Diabetes (T1D) and its Complications." The purpose of this RFA is to support the development of novel or improved therapeutics for the prevention and/or treatment of T1D and its complications as well as the development of new methods to monitor the initiation, progression and therapy of T1D and its complications. The use of animal models of diabetic neuropathy and its complications, developed through the AMDCC described above, would be important in many of the types of projects that this announcement seeks to encourage.

Item

Charcot-Marie-Tooth [CMT] - The Committee welcomes the upcoming NINDS workshop on peripheral neuropathies, and encourages NIH to focus on CMT in this workshop, with a goal of producing outcomes which will be directly relevant to CMT research. The Committee encourages all relevant institutes and centers, including NIAMS, NIDDK, and NICHD, to participate in the workshop. In addition, the Committee encourages NIH to incorporate CMT research into the Blueprint for Neurosciences initiative. (p. 73)

Action taken or to be taken

Charcot-Marie-Tooth disease (CMT) is one of the most common inherited neurological disorders, affecting approximately 1 in 2,500 people in the United States, and is part of a larger group of disorders called the peripheral neuropathies. CMT is caused by the degeneration of peripheral nerves due to a disruption of the structure or function of either the peripheral nerve axon or the "myelin sheath," a covering of protein and fatty substances produced by Schwann cells that insulates nerve fibers and prevents dissipation of the electrical signals.

The National Institute of Neurological Disorders and Stroke (NINDS) supports a wide range of studies to identify the genetic mutations which cause various forms of CMT, and to understand the process of myelination and its regulation. More broadly, NINDS supports research on other forms of peripheral neuropathy which may help in identifying potential treatments for CMT. In addition, other Institutes at NIH support research on genes and proteins that play a role in CMT.

The NINDS is planning a workshop for Spring 2006 on the peripheral neuropathies, and CMT, together with other inherited, infectious, and inflammatory neuropathies will be included. The purpose of the workshop is to identify and discuss research opportunities, needs, and gaps in our knowledge of the peripheral neuropathies in order to both improve our understanding of and develop potential therapies for these disorders. Because disease mechanisms may be shared among multiple types of neuropathies, this is an important time to bring together investigators working on diverse neuropathies. Rather than focus on each form of neuropathy as a separate entity, the workshop will strive to integrate researchers working on the different forms of peripheral neuropathy to discuss topics such as the molecular and cellular basis of disease,

diagnostic tools, treatment strategies, the natural history of the disorders, and clinical trial endpoint measures. This approach has proven to be a very successful format in previous workshops sponsored by NINDS, fostering collaborative discussions among researchers from different areas, giving them an opportunity to approach questions about their specific research from a different perspective, and identifying commonalities among the different disorders. NINDS-funded researchers working in CMT and other peripheral neuropathies, as well as those from other Institutes at the NIH with an interest in this area, will be invited to participate.

The NIH Neuroscience Blueprint is a collaborative effort across fifteen Institutes and Centers to accelerate the pace of discovery and understanding in neuroscience research. The Blueprint strategy is not designed to selectively target specific diseases, but rather to enhance the resources and research environment to broadly improve research and therapeutic development for neurological disorders. Blueprint initiatives that may be applicable and beneficial to CMT researchers include initiatives on gene mapping, neuroimaging, a microarray consortium, research facility core centers, and an inventory of neuroscience resources available to investigators.

Item

Traumatic brain injury (TBI) -- The Committee encourages NINDS to build upon basic and translational research in brain injury rehabilitation at the National Center on Medical Rehabilitation and Research (NCMRR). NCMRR has awarded grants to eight bench science research centers and a data center to establish the cooperative multi center traumatic brain injury clinical trials network. The Committee encourages NINDS to participate in supporting these centers and to support training grants for TBI researchers. (p.73)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) leads NIH traumatic brain injury (TBI) research and works closely with the NCMRR to ensure that their efforts against TBI complement one another. The extensive NINDS TBI program supports basic, translational, and clinical research and research training on TBI through grants and contracts to more than 100 individual investigators and multi-disciplinary research teams, including scientists at most of the institutions in the NCMRR TBI network. NINDS-supported basic studies are investigating the underlying mechanisms that contribute to immediate and delayed brain damage. Translational research is developing interventions in laboratory models of TBI to minimize brain damage that follows TBI and to promote recovery. Clinical studies are investigating the consequences of TBI in people and the mechanisms of recovery. All of these efforts ultimately feed into the Institute's longstanding program of clinical trials to test the safety and effectiveness of interventions to improve outcome from TBI. To expedite the development of emergency treatments for brain injuries and other neurological disorders, the NINDS has recently begun an Emergency Neurological Clinical Trials Network (ENCTN) that brings together scientists and physicians from emergency medicine, neurology, neurosurgery, and other disciplines. The NINDS also supports extensive research in cross cutting scientific areas such as stem cells, neural prostheses, brain imaging, regeneration, and brain plasticity that are important for developing better

treatment for TBI and other nervous system disorders and, when appropriate, cooperates with the NMRR to apply insights from this research to rehabilitation.

Training of TBI investigators for the future is a major priority of NINDS TBI programs. The majority of NINDS research grants on TBI also support the training of graduate students and post-doctoral fellows. In addition, the Institute supports training of future researchers in TBI through individual and institutional training programs tailored to the needs of M.D.'s, M.D.-Ph.D.'s, and Ph.D.'s. in basic and clinical research. These include pre- and post-doctoral fellowships and career development awards to individual trainees, as well as institutional training grants.

Item

Dystonia – The Committee continues to support research on the neurological movement disorder dystonia, given that dystonia is the third most common movement disorder after essential tremor and Parkinson's disease. The Committee encourages NINDS to support research on both focal and generalized dystonia, and to continue its study of the DYT1 gene. The Committee is pleased with progress made in expanding the dystonia research portfolio as a result of the joint dystonia research program announcement, and hopes that NINDS will consider options for continued progress once the program announcement expires in August 2005. (p. 73)

Action taken or to be taken

In 2002, the National Institute of Neurological Disorders and Stroke (NINDS), the National Eye Institute, the National Institute of Child Health and Human Development, and the National Institute on Deafness and Other Communication Disorders released a Program Announcement (PA) entitled "Studies into the Causes and Mechanisms of Dystonia." The NIH funded eleven grants as a result of this solicitation. These awards spanned a broad range of research areas, including gene discovery, the genetics and genomics of dystonia, the development of animal models of primary and secondary dystonia, molecular and cellular studies of inherited forms of dystonia, epidemiology studies and brain imaging. NINDS also awarded supplemental funding to two of these grants for the distribution and sharing of animal models. Generalized dystonia caused by mutation of the DYT1 gene is the focus of several grants awarded under the recent PA, and both intramural and extramural researchers are exploring the basis of and treatment options for generalized and focal dystonias. NINDS program staff are currently assessing how the PA has impacted the field, whether continuation is warranted, and if so, what areas would be important for the focus of a future solicitation. To this end, program staff participated in a workshop on "RNA Interference in Dystonia" in August 2005 and the Annual Bachmann-Strauss Dystonia and Parkinson's Disease Foundation's Think Tank in November 2005, using both meetings as opportunities to gather information on research needs for future programmatic planning. The NINDS is also partnering with the Dystonia Medical Research Foundation and other stakeholders in a joint scientific workshop in 2006 to further assess the critical research needs in the dystonia field.

Item

Spina bifida - The Committee strongly encourages NINDS to enhance research to address issues related to the outcome and recommendations of the 2003 Spina Bifida Research Conference. NINDS is urged to strengthen and prioritize research efforts in the prevention and treatment of spina bifida and associated secondary conditions, with a particular focus on improved treatment of hydrocephalus. The Director should be prepared to testify on its efforts to advance these areas of research at the fiscal year 2007 appropriations hearing. (p. 73)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) funds a wide range of research projects relevant to spina bifida and associated secondary conditions. Spina bifida is a neural tube defect caused by the failure of the fetus's neural tube- which forms the brain and spinal cord- to close during the first month of pregnancy. The May 2003 conference, "Evidence-Based Practice in Spina Bifida: Developing a Research Agenda," identified knowledge gaps and research priorities to improve care of individuals with spina bifida. Among the recommendations that emerged from the conference was improved assessment and treatment of hydrocephalus, a build up of fluids in the brain, that is associated with spina bifida.

The NINDS funds research on both preventing and treating hydrocephalus; in particular, NINDS-funded researchers are attempting to optimize shunts for the treatment of hydrocephalus and to develop an ambulatory system for the detection of shunt failure. In September 2005, the NINDS, together with the Office of Rare Diseases (ORD), the National Institute on Aging (NIA), the National Institute of Child Health and Human Development (NICHD) and the Hydrocephalus Association organized a workshop entitled "Hydrocephalus: Myths, New Facts, Clear Directions." Researchers studying mechanisms of hydrocephalus, risk factors, and related disorders came together to develop strategies for improving our understanding of hydrocephalus and identifying new collaborative opportunities for clinical tools and treatments.

The NINDS also funds grants to understand the genetic causes of spina bifida and to develop strategies to prevent the condition. Recently, NINDS-funded investigators conducted a genetic analysis of nearly 300 individuals from 44 families with neural tube defects. The analysis narrowed the hunt for the genes that cause neural tube defects to several gene clusters on chromosomes 7 and 10, which should help accelerate further gene discovery. Another project recently funded by NINDS is studying the underlying mechanisms by which folate reduces risk of neural tube defects, including the role of maternal and fetal folate-related genes. This is particularly important because folate supplementation has been shown to decrease the risk of spina bifida, however, the mechanisms underlying this decrease are not known. Another recently funded project is looking at gene and environment interactions that may play a role in neural tube defects in Guatemalan families, since Guatemala's prevalence of neural tube defects is among the highest in the world. Finally, NINDS also helped support the 4th International Conference Neural Tube Defects, held in September 2005. This conference brought together researchers in fields including genetics, epidemiology, molecular biology, and nutrition to share results and ideas, establish new collaborations, and identify new avenues of research.

The NINDS will continue to work with the other NIH Institutes with an interest in spina bifida research (the National Institute of Child Health and Human Development, the National Institute of Dental and Craniofacial Research, the National Institute of Environmental Health Sciences, the National Human Genome Research Institute, and the National Center of Research Resources) to further research progress in this area.

Item

Neurofibromatosis (NF) - Advances in NF research have linked NF to cancer, brain tumors, learning disabilities, memory loss and heart disease affecting millions of Americans. The Committee encourages NINDS to strengthen its NF clinical and basic research portfolios. The Committee commends NINDS for its leadership role in NF research and in coordinating efforts with other Institutes engaged in NF research. The Committee recognizes that basic research has now successfully brought NF research into the clinical era. The Committee encourages NINDS to continue its exemplary efforts in the creation, implementation and funding of NF clinical trials infrastructures and clinical trials using existing and new drugs on NF patients. The Committee hope that NINDS will continue to coordinate its efforts with the other institutes at NIH as well as other government agencies. (p. 74)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) continues to work closely with other NIH institutes as well as other federal agencies toward the development of neurofibromatosis (NF) treatments. In September 2004 NINDS, in collaboration with the Office of Rare Diseases at NIH and the Department of Defense (DoD), sponsored a meeting to identify the key barriers to NF clinical research and strategies to overcome them. Through this meeting, NINDS assisted the DoD in developing a strategy for building infrastructure for clinical trials in NF and advised them about how the proposed infrastructure could best be coordinated with existing and planned NINDS funding efforts. The DoD is currently requesting applications for the development of a data coordinating center and clinical research sites interested in conducting clinical trials in NF. The NINDS will continue to participate in the planning of this new NF consortium dedicated to overcoming barriers to clinical trials in NF and anticipates that the consortium will serve as a useful resource for the NF community.

In FY 2004, the NINDS, in collaboration with the National Institute of Deafness and Other Communication Disorders, issued a program announcement (PA) for the establishment of National Centers for Neurofibromatosis Research that will capitalize on recent basic, translational, and clinical research advances to develop therapies for NF patients. National Centers will serve as centralized collections of resources and will facilitate the interactions between basic scientists and clinicians necessary for effective basic research, pre-clinical therapy development, and clinical studies and trials. In 2005, NINDS funded the first Center, established jointly at the University of Texas Southwestern Medical Center and Indiana University. The Center will investigate the molecular and cellular consequences of mutations in the NF1 gene, the underlying cause of neurofibromatosis type 1 (NF1), and their role in the formation of two of the most common tumors in NF1, gliomas and neurofibromas. The Center will also investigate

if FDA approved therapies are effective at interrupting cell-to-cell interactions that may contribute to neurofibroma formation.

Item

Spinal muscular atrophy (SMA) - SMA is the leading genetic killer of infants and toddlers. The Committee understands that the severity of the disease, its relatively high incidence, and the possibility of imminent treatments have led NINDS to initiate the SMA Therapeutics Development Program. The Committee commends NINDS for this initiative and encourages the Institute to continue to commit the resources to ensure a timely completion of the project to identify and complete preclinical research and development of candidate therapeutics for treating SMA by 2007. To maximize program efficiency, it is also important that NINDS lead efforts to integrate therapeutics development efforts with emerging programs in the biotech and pharmaceuticals industry, academic medical centers and collaborations with voluntary health organizations to ensure that duplication of effort is avoided. The Committee understands that the strategy for developing a treatment for SMA will guide therapeutics development for other diseases including Duchenne muscular dystrophy, ALS, Huntington's and Alzheimer's. (p. 74)

Action taken or to be taken

The NINDS is continuing its commitment to the SMA Project's ambitious goal of bringing a drug for SMA to readiness for clinical trials by the end of 2007. The project has established a highly qualified and heavily engaged steering committee, with expertise in drug development from industry, the FDA, academia and the NIH. The group has developed a detailed drug development plan and is implementing the plan. The Project has identified compounds that have sufficient effectiveness in SMA model systems and appropriate chemical characteristics to serve as leads for developing a drug. The Project has also established the tools and facilities for systematically modifying these leads, testing the newly generated drug candidates in cell and animal models, handling the substantial informatics requirements, and coordinating the overall drug development scheme. The drug development process is now underway, with more than 300 new compounds already synthesized. Through the steering committee and the active efforts of the NINDS Director and staff, the SMA Project is seeking appropriate collaborations, including meetings with academic groups, non-governmental organizations, and companies . Toward that end, in September 2005, the SMA Project Steering Committee met with representatives of non-profit organizations focused on SMA to discuss opportunities for enhancing those interactions as the project moves forward.

The SMA Project is itself an experiment. As the project moves forward, the NINDS is evaluating what can be learned from the project to expedite therapy development for other diseases. In fiscal year 2007, the Institute plans to provide resources for medicinal chemistry to other diseases based on a component of the SMA Project. Medicinal chemistry is an essential step in drug development that performs systematic chemical changes on promising "lead compounds" to improve their effectiveness, side effects, brain absorption, and other drug like characteristics.

Item

Down Syndrome - The Committee commends NINDS for sponsoring a down syndrome workshop to address research priorities relating to optimizing synaptic structure and function in neuronal circuits important for cognition. The Committee encourages NINDS to identify opportunities for investigating the genetic and cellular basis for abnormalities in the structure and function of these circuits in both the developing and mature nervous system. NINDS is also encouraged to work with NIA to develop strategies to investigate the biology of age-related disorders, such as Alzheimer's disease and Parkinson's disease, in people with Down syndrome. NINDS is also encouraged to work with the Office of the Director to develop a strategic plan for Down syndrome research and to coordinate its research with NICHD, NIA, NIMH and other institutes. (p. 74)

Action taken or to be taken

Down syndrome is the most common genetic cause of mental retardation, occurring in 1 in 800 live births. The syndrome is caused by the inheritance of an extra copy of chromosome 21, leading to the abnormal expression of hundreds of genes located on this chromosome. In addition to having cognitive deficits and characteristic facial features, individuals with Down syndrome also frequently exhibit early-onset Alzheimer's disease and a number of other medical conditions. The National Institute of Neurological Disorders and Stroke (NINDS) is sponsoring an investigation into the identity and brain distribution of abnormally expressed proteins in a mouse model of Down syndrome. This study may help to identify critical proteins and cellular processes that are altered in response to the chromosome abnormality. In addition, NINDS also supports other research areas of relevance to Down syndrome. For example, NINDS supports a number of studies focused on understanding the pathophysiology of protein deposits called amyloid plaques, which are seen in Alzheimer's disease but are also found before the onset of dementia in Down syndrome. Advances in understanding the development and prevention of amyloid plaques may provide benefits for both Alzheimer's disease and Down syndrome. The NINDS will also work with the National Institute on Aging (NIA) to explore opportunities related to understanding the biology of Parkinson's Disease in Down syndrome patients.

The NINDS also works closely with the National Institute of Child Health and Human Development (NICHD), the National Institute on Mental Health (NIMH) and the National Institute on Aging (NIA) to identify areas of Down syndrome research in need of particular attention. In February 2005, the NINDS, together with NICHD, NIMH and NIA, sponsored a workshop entitled: "Down Syndrome: toward optimal synaptic function and cognition." The goal of the workshop was to identify neuronal signaling processes that underlie the cognitive abnormalities seen in Down syndrome and might eventually serve as therapeutic targets in Down syndrome. A number of research needs were identified at the meeting, including new animal models of Down syndrome, patient registries, DNA and tissue banks, and standardized assays of cognitive function. The NINDS and the other institutes are currently discussing ways to best address these issues and facilitate further research on Down syndrome. In addition, the NINDS will work together with the NICHD, the lead Institute for Down syndrome, and other Institutes as appropriate to establish priorities in Down syndrome research and coordinate research efforts.

Item

Mucopolysaccharidosis (MPS) —The Committee commends NINDS efforts in the development and release of a program announcement to enhance blood brain barrier research in lysosomal storage disorders. The Committee continues to encourage NINDS to collaborate with all appropriate Institutes and Centers to support ongoing MPS research, including study of the blood brain barrier as an impediment to treatment, and to use all available mechanisms to further stimulate efforts to better understand and treat MPS disorders. (p. 74)

Action taken or to be taken

The NINDS promotes mucopolysaccharidosis (MPS)-related research through a variety of different mechanisms. The MPS portfolio currently includes projects that focus on gene transfer and stem cell transplantation as potential therapeutic approaches. In addition, the NINDS and NIH Office of Rare Diseases (ORD) recently awarded a new grant on MPS and the blood-brain barrier under the July 2004 program announcement entitled "CNS Therapy Development for Lysosomal Storage Disorders." This FY06 grant will enable a well-established investigator to test a new strategy for delivering therapeutic enzymes across the blood-brain barrier in mouse models of MPS I, IIIB, and VII. The work follows the results of a pilot study, funded through the NINDS translational research program. The NINDS recently reissued the program announcements for this translational research program, which encourages therapy development for neurological disorders. The NINDS also has an active program announcement on the blood-brain barrier. Grant applications may focus on the biology of the blood-brain barrier or delivery strategies for therapeutics. As always, NINDS welcomes creative research proposals on MPS that are not linked to particular solicitations.

In addition to funding research on MPS, the NINDS also stimulates the field through support of scientific meetings. The NINDS is sponsoring a workshop in April 2006 on gangliosides, substances that accumulate in some tissues of MPS patients and contribute to MPS symptoms. The NINDS is also working with the MPS Society to organize a workshop on clinical tools required for MPS trials. This second workshop is scheduled for the spring of 2007.

Item

Fragile X - Fragile X is a single-gene disorder, but both its symptoms and its cellular mechanisms suggest involvement of multiple genes and specific brain pathways which are associated with other neurological disorders, such as autism and seizures. Recent research offers clear evidence of disruption of fundamental brain circuitry in Fragile X. Thus, Fragile X research has the potential to contribute to the understanding of multiple disorders, such as seizure disorders, especially in the context of developmental disorders, and autism. The Committee encourages NINDS to intensify its research into these issues as they relate to Fragile X, and to coordinate this research with other institutes working on Fragile X, including but not limited to NIMH and NICHD. (p. 75)

Action taken or to be taken

The National Institute of Neurological Disorders and Strokes (NINDS) supports research to characterize the neurophysiological basis of Fragile X syndrome (FXS). The disease is associated with a mutation in a single gene located on the X chromosome, leading to a lack of expression of the Fragile X Mental Retardation Protein (FMRP). The NINDS funds several grants aimed at understanding the roles of FMRP in shaping neuron and brain development and FMRP's role in the neuronal connections that underlie learning. The NINDS also funds grants characterizing mice and fruit fly models of FXS, with the long-term goal of developing better therapies. In fact, a recent NINDS-funded study showed that drugs which block one class of glutamate receptors improved the memory deficits in the fly model of FXS.

Individuals with FXS often have comorbid neurological or neuropsychiatric conditions, such as seizures and autism. Approximately 20% of children with FXS have epilepsy, although in most cases seizures can be controlled with currently available therapies. The NINDS supports a large portfolio of research on epilepsy, including studies to prevent the development of epilepsy in those at risk for the disease, which may be helpful in understanding and preventing seizures in children with Fragile X. In addition, approximately 15% to 25% of children with FXS are diagnosed with autism. Researchers have argued that autism and autistic symptoms in FXS reflect a common etiological or pathophysiological pathway underlying the two conditions. To encourage research in this area, the NINDS, the National Institute of Mental Health and the National Institute of Child Health and Human Development have entered into a public-private partnership with the Canadian Institutes of Health Research, Ireland's Health Research Board, Cure Autism Now, the National Alliance for Autism Research, Autism Speaks and the FRAXA Research Foundation to issue a Program Announcement called "Shared Neurobiology of Fragile X Syndrome and Autism." The announcement, released in May 2005, encourages investigators to submit research proposals aimed at characterizing, understanding and treating etiological and pathophysiological mechanisms common to both Fragile X syndrome and autism.

Item

FXTAS- Fragile X-associated tremor/ataxia syndrome, or FXTAS, is a newly discovered, progressive neurological disorder that affects older men who are carriers of a premutation in the same gene that causes Fragile X syndrome. Nearly 1 in 800 men in the general population carries this premutation and as many as 30 percent of these carriers--roughly 1 in 3,000 men--may develop FXTAS later in life. Identification of older male carriers will lead to a better understanding of the true incidence of Fragile X syndrome and afford at-risk families of child-bearing age the opportunity to pursue genetic counseling. NINDS, in collaboration with NIA, is urged to strengthen research into FXTAS, including working with the other NIH institutes. (p. 75)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports a variety of investigator-initiated research projects on Fragile X syndrome and on Fragile X-associated Tremor/Ataxia Syndrome (FXTAS). Fragile X syndrome is caused by a gene mutation, called a

repeat expansion mutation, which adds a long stretch of abnormal DNA to the genetic sequence. If the repeat expansion is long enough to cause a complete loss of function in the gene product - the Fragile X Mental Retardation Protein (FMRP) - Fragile X syndrome results. In the case of FXTAS, the repeat expansion is called a premutation because is not quite long enough to cause Fragile X syndrome. However, late-onset motor abnormalities and cognitive decline in a subgroup of older men who carry the Fragile X premutation suggest that even the smaller repeat expansion alters the function of the FMRP protein and causes neurological symptoms. More recently, a milder form of the syndrome has also been found in female premutation carriers.

Two clinical research projects funded by NINDS are focused on identifying the neurological alterations in carriers of the premutation associated with FXTAS. Together, these studies will provide information about the clinical features of this newly-recognized disorder, including the rate of progression, and the relationship between the gene abnormality and the severity of FXTAS symptoms. Misdiagnosis of FXTAS may also present a challenge for optimal treatment and care of FXTAS patients. Indeed, investigators supported by NINDS and the National Institute of Child Health and Human Development recently reported a study of 56 FXTAS patients, most of whom received multiple misdiagnoses before being identified as having FXTAS. Incorrect diagnoses were often in the categories of parkinsonism, tremor, ataxia, dementia, or stroke. These investigators suggested new guidelines to facilitate proper diagnosis of FXTAS, which should improve estimates of the incidence of the disease and facilitate genetic counseling. The NINDS continues to support a number of basic research studies into the function of the normal and pathological FMRP protein in order to provide a foundation for translational and clinical research on effective treatment strategies for FXTAS.

Item

Frontotemporal Dementia – The Committee encourages NINDS to support research into drug discovery efforts that focus on specific targets relevant to treating the mechanisms underlying brain degeneration due to frontotemporal dementia (FTD) such as Pick's disease. The Committee is interested in research that will focus on methods for discovering the causes of this family of diseases, improving diagnostic accuracy, and providing longitudinal characterizations so that the success of intervention can be determined. (p. 75)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS), along with the National Institute on Aging (NIA), and several other Institutes at the National Institutes of Health (NIH), recognize that Pick's disease and other frontotemporal dementias (FTDs) represent a broad group of conditions that are both distinct from other forms of dementia, like Alzheimer's disease, but which bear many cellular and clinical similarities to a range of other neurodegenerative conditions. Consistent with the collaborative spirit at the NIH, the NINDS initiated an Inter-institute FTD working group in October 2005, which will ensure that Institutes and Centers funding FTD research are functioning cooperatively on as many projects as possible, and are eliminating any duplication of effort.

With regard to drug discovery and other translational research efforts, the NINDS and NIA are engaged in a number of programmatic activities that are critical to the future development of treatment trials. For example, both Institutes have supported the development of assays, or tests, which can be used to assess the ability of potential therapeutic compounds to reduce the abnormal development of cellular structures called neurofibrillary tangles in FTD and related conditions. This research has led to the identification of promising compounds and the development of plans to continue the screening of additional drugs and the testing of these potential therapies in animal models with neurofibrillary pathology. The ultimate goal of these future studies is the identification of one or more compounds that may be moved into clinical trials.

In addition, the NIA supports research on the FTDs at four of its Alzheimer's Disease Research Centers, and provides funding for investigators with projects relevant to Pick's and other FTDs. For example, the NIA is currently supporting a multi-year study of people with a form of FTD, in order to characterize the natural course of disease, develop a cognitive test instrument that is specific for this type of FTD, and determine whether specific genetic changes are associated with the rate of disease progression or other cognitive, behavioral, or anatomical changes. The goal of this data collection is to lay the groundwork and develop the tools that would be necessary to carry out a clinical trial of drug therapy for people with FTD.

In addition to providing support for these translational studies, both Institutes fund a wide range of basic science research projects that are relevant to developing a better understanding of the FTDs. For example, they support multiple studies of tau, a structural protein that is significantly altered in individuals with FTD, and its impact on neurodegeneration. They also support studies on the effects of FTD on cognition, speech, mental and social function, as well as diagnosis of the FTDs using neuroimaging techniques. Furthermore, both the NINDS and the NIA are working with the extramural community to develop a conference that would address the next steps for basic science research on the FTDs and the translation of the most promising of these findings into clinical studies.

FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 109-103)

Item

Alzheimer's Disease – NINDS is currently supporting both pre-clinical and translational research intended to expand the pool of therapeutic agents for treating Alzheimer's disease. For example, a recent NINDS-supported study tested a drug that interferes at a specific point in the cholesterol pathway that contributes to the generation of amyloid protein, a hallmark of Alzheimer's. The study resulted in a 99 percent reduction in brain amyloid in a mouse model of the disease, suggesting that this may provide a novel approach for developing a therapeutic intervention for Alzheimer's disease. The Committee encourages NINDS to continue to assign a high priority to Alzheimer research, and to work closely with NIA, NIMH and other institutes. (p. 110)

Action taken or to be taken

Please refer to page NINDS - 36 of this document for the NINDS response to this significant item regarding Alzheimer's disease.

Item

Amyotrophic Lateral Sclerosis (ALS) - The Committee is pleased by the increased number of NINDS research programs on ALS, including participation in the NIH partnership of 14 Institutes to accelerate neuroscience research, the NIH Blueprint for Neuroscience Research, plus new interdisciplinary collaborations with other organizations and appropriate NIH Institutes, particularly NIEHS. The Committee commends NINDS on its multiple initiatives involving high-throughput screening and assay development to identify compounds with activity in neurodegenerative disorders, including ALS. The Committee is gratified by the development of translational research and the clinical trials programs at NINDS and by the public's new opportunities to benefit from better access to and dissemination of information. The Committee is also pleased by the series of scientific workshops held since 2003 with the Department of Veterans Affairs [VA], the Department of Defense [DOD], and with leading scientists from academic centers throughout the Nation. The Committee encourages NINDS to continue and to grow its collaborative initiatives with voluntary health associations, other NIH Institutes, the DOD and the VA in the effort to advance ALS research and identify treatments and a cure for the disease. (p. 111-112)

Action taken or to be taken

The NINDS continues to work actively with multiple facets of the ALS research and patient communities, including other NIH Institutes and Centers, other governmental agencies, and non-governmental organizations that support ALS research. As one specific example, the NINDS established a repository for DNA and other genetic material in 2002. The goal of this repository was to facilitate the free exchange of these valuable research materials throughout the community, at a very reduced cost. To date, the response from the ALS research community has

lagged behind other fields, and NINDS has worked aggressively with leaders in the ALS community, as well as with contacts at the ALS Association (ALSA), to accelerate deposits from individuals with ALS and other motor neuron diseases. In addition, NINDS staff have recently reached an agreement with two top ALS geneticists to deposit their genetic samples into the NINDS repository. NINDS anticipates that together, these efforts will lead to a significant increase in the deposition of samples in the coming year. As a second example, NINDS has collaborated with ALSA on the support of drug studies in the ALS mouse model that were crucial for FDA acceptance of the current clinical trial of ceftriaxone for ALS. Lastly, NINDS has partnered with ALSA to evaluate and prioritize neuroprotective agents and other potential therapies for future trials in ALS through ALSA's "Translational Research Advancing Therapy for ALS" (TREAT-ALS) program. The NIH Rapid Access to Interventional Development program – a component of the NIH Roadmap intended to reduce some of the common barriers between laboratory discoveries and clinical trials of new therapeutic entities – is a potential resource for supporting the late-stage pharmacology/toxicity studies for ALS drugs that are currently being developed through the TREAT-ALS activities, and NINDS anticipates providing co-funding of any applications that are successful in securing Roadmap funds for these projects.

In addition to these collaborative efforts, NINDS has also made significant headway into facilitating the innovative design of clinical trials, which can improve the efficiency of the process for conducting and evaluating early stage clinical trails, and allowing them to proceed to efficacy studies. As a recent example, program staff from the NINDS Clinical Trials Group worked with extramural investigators to design a multi-stage clinical trial of ceftriaxone for ALS, so that funding of the phase III trial can proceed without an intervening application if the pilot phase is successful. This design should accelerate completion of the study and a determination of ceftriaxone's efficacy by at least two years. Time savings of this magnitude are particularly critical for individuals with ALS, who are experiencing a rapid loss of neurons and decline in function.

NINDS also recognizes the interest in the ALS community in developing a patient registry. NINDS has discussed the possibility of establishing a registry with ALSA, and are currently in discussions with staff from the Department of Veterans Affairs regarding the coordination of efforts for this type of project.

Item

Ataxia-Telangiectasia (A-T) - A-T is a genetic disease that attacks in early childhood. It progressively affects coordination and severely compromises the immune system. Children with A-T are highly likely to develop cancer, and rarely live beyond their teens. The Committee encourages the NINDS to work with NCI and other appropriate Institutes to support research aimed at understanding the underlying causes of A-T, with the goal of translating this basic research into treatments for the disease (p.111)

Action taken or to be taken

Since A-T is a disease that affects many different organ systems, coordination across NIH Institutes and Centers is crucial for progress. The NINDS recently initiated the creation of the

Trans-NIH A-T Research Working Group, which includes program directors from the NINDS, National Cancer Institute (NCI), Office of Rare Diseases (ORD), and eleven other Institutes. This working group has met to review the NIH A-T research portfolio and outline goals for an A-T research plan. The plan is now in the final stages of development.

The members of the Trans-NIH A-T Research Working Group fund basic research to understand the molecular mechanisms underlying A-T and more directed efforts to develop therapies. NIH funding contributed to the 1995 identification of the disease gene, *ATM* (Ataxia-Telangiectasia, Mutated). This gene encodes a protein responsible for repairing damaged DNA. The NINDS currently supports research to understand how ATM protein mediates DNA repair and how lack of functional ATM eventually contributes to the neurological symptoms of A-T. The NINDS also supports efforts aimed at translating basic mechanistic information into potential therapies. For example, NINDS-funded researchers are conducting preclinical experiments on drugs that can trick cultured cells with mutated *ATM* to ignore the mutations and express functional ATM protein. Another laboratory is exploring possibilities for gene therapy, and yet another group is developing a rhesus monkey model of A-T that can be used to test potential therapies.

The NINDS also tries to accelerate progress in A-T research by supporting scientific meetings. This past year, NINDS funded a workshop to develop a high-throughput drug screening strategy for A-T and co-sponsored an International Scientific Conference on A-T that brought together scientists working on a variety of relevant topics, including DNA repair, cell metabolism, neurodegeneration, immunology, and cancer development. The NINDS is also planning a workshop in FY 2006 on clinical research in A-T.

Item

Basic Behavioral and Social Sciences Research- The Committee encourages NINDS to participate in trans-institute initiatives organized by OBSSR or another institute to strengthen basic behavioral research and enhance opportunities for behavioral science research training. (p. 111)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports a broad portfolio of basic behavioral research, which includes studies on a variety of cognitive and behavioral processes. Examples include studies to examine the cellular and molecular mechanisms of learning and memory, to explore the neural bases of language and cognitive development, and to understand the neural substrates of decision-making. NINDS also sponsors a wide range of training grants, fellowships, and career development awards in all areas of the neurological sciences, including basic behavioral and social science research.

NINDS has partnered with the Office of Behavioral and Social Sciences Research (OBSSR) as well as other NIH Institutes and Centers on a number of initiatives. In January 2003, OBSSR, NINDS, and 14 other NIH Institutes and Centers, issued a request for applications for exploratory/developmental research focused on "Mind-Body Interactions and Health." This announcement encouraged research exploring the relationship between behavioral /psychosocial

processes and physical health / biological processes. NINDS manages two grants funded as a result of this initiative. In July 2003, ten NIH Institutes and Centers, including NINDS, released the program announcement (PA) "Biobehavioral Pain Research" to stimulate research on pain at the interface of biology and behavior. In addition, in September 2003, seven NIH Institutes, including NINDS, issued the PA, "Basic and Translational Research in Emotion," to encourage research on the processes and mechanisms involved in the experience and expression of emotion. NIH also released a notice in April 2005 announcing the availability of one-year administrative supplements to stimulate interdisciplinary research that integrates the behavioral or social sciences with the biological sciences. This was developed as an NIH Roadmap initiative.

Since many of the technologies for acquiring and analyzing data in behavioral science research require extensive time, labor, and cost, there is a need for new technologies that can make data collection more efficient. To encourage the development of these technologies, NINDS and the National Institute of Mental Health (NIMH) jointly sponsored a PA under the Small Business Innovation Research (SBIR) Program entitled "High Throughput Tools for Brain and Behavior," in April 2004. In addition, in April 2005, OBSSR, NINDS, and other NIH Institutes and Centers issued the PA, "Methodology and Measurement in the Behavioral and Social Sciences." The purpose of this announcement is to encourage research that will improve the quality and scientific power of data collected in the behavioral and social sciences. NINDS and OBSSR also participate, along with 13 other NIH Institutes and Centers, in the NIH Neuroscience Blueprint, a collaborative effort at NIH to accelerate neuroscience research by providing the tools and technologies necessary to accelerate progress. A number of Blueprint initiatives may be applicable and beneficial to researchers working in basic behavioral and social sciences research.

In an exciting trans-NIH initiative called "Cognitive and Emotional Health: The Healthy Brain Project," NINDS, NIMH, and National Institute on Aging (NIA) have joined efforts to assess the state of longitudinal and epidemiological research on demographic, social, and biologic determinants of cognitive and emotional health in aging adults.

The NINDS will continue to pursue opportunities for collaboration with OBSSR and other NIH Institutes and Centers, as appropriate, to strengthen research and training in this area.

Item

Batten Disease - The Committee strongly urges the Institute to increase funding for Batten disease research by actively soliciting grant applications and taking aggressive steps to assure that a vigorous research program is established. The Committee expects to be informed of the steps taken to increase research on Batten disease (p. 111)

Action taken or to be taken

The NINDS supports a variety of projects on Batten disease (also known as Neuronal Ceroid Lipofucinoses), including studies of the molecular pathway underlying the disease, the effects of the disease at the cellular and subcellular levels, the development of animal models, and preclinical testing of potential therapies. Most of these grants were investigator-initiated, but two new grants resulted from an aggressive effort by NINDS to encourage therapy development.

NINDS recently awarded a large cooperative agreement grant on Batten disease through its broad translational research program. The five research teams supported by this grant will conduct all the prerequisite studies for a gene therapy clinical trial in Batten disease. The researchers have established a series of milestones over the course of the five-year grant period, and NINDS program staff will carefully monitor progress. The NINDS and NIH Office of Rare Diseases (ORD) are also co-funding a new grant under a therapy development initiative specifically for lysosomal storage diseases like Batten. The grant will enable researchers to develop a new technology for therapeutic enzyme delivery, a major challenge in treating lysosomal storage diseases. This initiative represents a promising new approach to public-private partnerships: applications received under the program announcement that are not funded by NIH may be funded by the Lysosomal Storage Disease Research Consortium, comprised of at least six patient support groups and private family research foundations. The program announcement (with set-aside funds) will remain active until November, 2007.

The NINDS also stimulates new research ideas by supporting scientific conferences. The NINDS, Office of Rare Diseases (ORD), and National Institute of Child Health and Human Development (NICHD) co-sponsored the 10th International Conference on Neuronal Ceroid Lipofucinoses in June 2005. This meeting brought together physicians, scientists, and patients to discuss advances, challenges, and opportunities in Batten research. The meeting addressed the molecular basis of the disease and potential treatments, including stem cell, gene, nutritional, and drug therapies. The NINDS is also working with the organizing committee to plan for the 11th International Conference in 2007.

Item

Brain tumors —The Committee continues to believe that additional attention should be given by NINDS to identifying causes of and treatments for brain tumors and encourages NINDS to continue working with NCI to carry out the recommendations of the Report of the Brain Tumor Progress Review Group. (p. 111)

Action taken or to be taken

Brain tumor research continues to be a priority of the National Institute of Neurological Disorders and Stroke (NINDS), and the Institute is supporting a variety of activities that address recommendations in the Brain Tumor Progress Review Group (BT-PRG). A complicating feature of many brain tumors is the diffuse way in which they spread throughout the brain, making complete surgical removal difficult. The BT-PRG identified the need to understand brain tumor growth and migration in order to develop new therapies to arrest tumor dispersal. In March 2004, NINDS and the National Cancer Institute released a Program Announcement with set-aside funding (PAS) to promote the understanding and prevention of brain tumor cell migration. One project funded through this PAS will investigate the molecular mechanisms of tumor growth and evaluate the ability of an FDA-approved drug to inhibit tumor growth. A second grant will identify genes involved in tumor migration and infiltration as potential targets for future therapies.

The role of the blood-brain barrier (BBB) and the blood-tumor barrier (BTB) in treating brain tumors was also identified as a high priority by the BT-PRG. The inability of molecules to traverse the BBB or the BTB and reach the tumors hampers the effectiveness of many potential therapies. The NINDS has supported two recent initiatives on the blood-brain barrier and the neurovasculature of the brain. A new grant awarded under one of these initiatives will enable investigators to explore the role of a gene associated with chemotherapy resistance in the regulation of molecules across the BBB, leading to better strategies to enhance drug availability in the brain.

NINDS-funded investigators also are conducting research to identify tumor suppressor genes in gliomas (a class of brain tumors that are notoriously difficult to treat), develop gene therapies for gliomas, and engineer vaccines against brain tumors. The vaccine research is particularly compelling, given a recent breakthrough for treating glioblastoma multiforme, an aggressive type of brain tumor that often develops drug resistance during conventional chemotherapy treatment. The NINDS-funded investigators first administered a vaccine that stimulated the immune system to destroy the subset of the tumor cells that tend toward drug resistance. The investigators then treated the remaining tumor cells with conventional chemotherapy. The patients in preliminary studies responded well to the vaccine and chemotherapy combination, with some patients' tumors no longer visible via magnetic resonance imaging (MRI).

Item

Charcot-Marie-Tooth Disease - The Committee continues to be concerned about NIH support for research on Charcot-Marie-Tooth [CMT] disease. The Committee welcomes the upcoming NINDS workshop on peripheral neuropathies, but remains unclear as to the degree this workshop will focus on CMT. The Committee urges the NIH to include a significant focus on CMT in the upcoming workshop with a goal of producing outcomes which will be directly relevant to CMT research and lead to a relevant program announcement or request for applications on CMT. The Committee encourages that relevant Institutes and Centers will participate in the workshop. In addition, the Committee requests NIH incorporate CMT research into its Blueprint for the Neurosciences initiative. (p. 111)

Action taken or to be taken

Please refer to page NINDS - 42 of this document for the response to this significant item regarding Charcot-Marie-Tooth disorder.

Item

Down Syndrome - The Committee commends NINDS for sponsoring a Down Syndrome Workshop to address research priorities relating to optimizing synaptic structure and function in neuronal circuits important for cognition. The Committee encourages NINDS to identify opportunities for investigating the genetic and cellular basis for abnormalities in the structure and function of these circuits in both the developing and mature nervous system. In addition, NINDS is encouraged to develop strategies to understand the incidence and impact on cognition of obstructive sleep apnea and other disorders of sleep. The NINDS is also encouraged to work with

the NIA to develop strategies to investigate the biology of age-related disorders, such as Alzheimer's disease and Parkinson's disease, in people with Down syndrome. NINDS is also encouraged to work with the Office of the Director to develop a strategic plan for Down syndrome research and to coordinate its research with NICHD, NIA, NIMH and other institutes. (p. 112)

Action taken or to be taken:

Down syndrome is the most common genetic cause of mental retardation, occurring in 1 in 800 live births. The syndrome is caused by the inheritance of an extra copy of chromosome 21, leading to the abnormal expression of hundreds of genes located on this chromosome. In addition to having cognitive deficits and characteristic facial dysmorphology, individuals with Down syndrome also frequently exhibit early-onset Alzheimer's disease and a number of other medical conditions. The National Institute of Neurological Disorders and Stroke (NINDS) is sponsoring an investigation into the identity and brain distribution of abnormally expressed proteins in a mouse model of Down syndrome. This study may help to identify critical proteins and cellular processes that are altered in response to the chromosome abnormality. Another area of NINDS research is focused on understanding the pathophysiology of protein deposits called amyloid plaques, which are seen in Alzheimer's disease but are also found before the onset of dementia in Down syndrome. Advances in understanding the development and prevention of amyloid plaques may provide benefits for both Alzheimer's disease and Down syndrome. The NINDS will also work with the National Institute on Aging (NIA) to explore opportunities related to understanding the biology of Parkinson's Disease in Down syndrome patients.
In addition, individuals with Down syndrome may be at increased risk for sleep disturbances, especially sleep apnea. The NINDS also supports a large portfolio of research projects on sleep disorders and circadian rhythms. This includes studies on sleep apnea and on the relationship between sleep, sleep deprivation, and cognitive function.

The NINDS also works closely with the National Institute of Child Health and Human Development (NICHD), the National Institute on Mental Health (NIMH) and the National Institute on Aging (NIA) to identify areas of Down syndrome research in need of particular attention. In February 2005, the NINDS, together with NICHD, NIMH and NIA, sponsored a workshop entitled: "Down Syndrome: toward optimal synaptic function and cognition." The goal of the workshop was to identify neuronal signaling processes that underlie the cognitive abnormalities and might eventually serve as therapeutic targets in Down syndrome. A number of research needs were identified at the meeting, including new animal models of Down syndrome, patient registries, DNA and tissue banks, and standardized assays of cognitive function. The NINDS and the other institutes are currently discussing ways to best address these issues and facilitate further research on Down syndrome. In addition, the NINDS will work together with the NICHD, the lead Institute for Down syndrome, and other Institutes as appropriate to establish priorities in Down syndrome research and coordinate research efforts.

Item

Duchenne Muscular Dystrophy - The Committee remains concerned with the amount of time taken by the NIH to comply with requirements of the MD Care Act, which became law in

December 2001. However, the Committee is pleased NIH has funded one additional Wellstone Muscular Dystrophy Cooperative Research Center and is working to fund two more for a full complement of six. The Committee further encourages the Institute to provide adequate funding and resources for each center. The Committee further requests that NINDS coordinate with NIAMS on timelines for translational research, the consensus conference and the strategic plan. (p. 112)

Action taken or to be taken

The NIH has been actively implementing the provisions of the MD-CARE Act including establishing and convening the Muscular Dystrophy Coordinating Committee (MDCC), developing a research and education plan for muscular dystrophy (MD), establishing the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, and developing a broad-based research grant portfolio in the muscular dystrophies.

The MDCC has met four times, and has developed –with input from a scientific working group- the MD Research and Education Plan. In accordance with the Act, this Plan was submitted to Congress in August 2004, one year after all members of the Committee were appointed. A second scientific working group was convened in August 2005 to refine the Plan and to develop and prioritize specific aims for the entire MD community. The resulting "Action Plan for the Muscular Dystrophies," was reviewed by the MDCC at its most recent (November 9, 2005) meeting. The Action Plan emphasizes the need for interagency and external collaborations to improve the detection, diagnosis, treatment, and prevention of all of the muscular dystrophies. NINDS will work closely with other NIH Institutes, including NIAMS and NICHD, and with other agencies and MD-focused organizations to implement the goals of the Action Plan.

NIH funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers. In response to the first Request for Applications (RFA), NIH funded three Centers in October 2003 -- at the University of Rochester (funded by NINDS), the University of Pittsburgh, and the University of Washington. The RFA was re-issued in March 2004, and NINDS funded an additional Center at the University of Iowa in early FY 2005. Following resubmission and further review of applications, NIH funded two more centers – at the University of Pennsylvania and Children's National Medical Center, for the full complement of six.

To enhance the activities at the Wellstone Centers, NIH recently released two notices announcing the availability of administrative supplements. The first, the "Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships," supports junior investigators affiliated with the Centers. The second notice, announcing support for Muscular Dystrophy Workshops and Research Conferences, encourages the Directors of the Centers, in collaboration with other MD researchers and/or representatives from voluntary health organizations, to apply for supplements to support small workshops focused on specific topics in MD research.

NIH also recently released two program announcements, both with set aside funds and a special grant application review environment, for "Translational Research in Muscular Dystrophy." The purpose of these initiatives is to implement a broad-based translational research program of exploratory/ developmental research projects and cooperative agreements. Translational

research was also a central focus of the November 9, 2005 MDCC meeting, where MDCC representatives presented their agency or organization's programs in translational research for the muscular dystrophies. Future MDCC efforts will be directed toward coordinating the various translational research activities in order to maximize the efficient use of resources while minimizing overlap.

Item

Epilepsy - The Committee seeks intensified efforts by the NINDS to produce breakthroughs in the prevention, treatment, and eventual cure of epilepsy. The Committee applauds the development of benchmarks for epilepsy research resulting from the `Curing Epilepsy: Focus on the Future' conference held in March 2000 and encourages the Institute to address important research issues raised at the `Living Well with Epilepsy II' conference held in July 2003. The Committee encourages NINDS to continue to dedicate resources for carrying out its benchmark priorities, to develop plans and goals for the anti-epileptic drug development program, and to report to the Committee on its activities to further these important areas of research. (p. 112)

Action taken or to be taken

Please refer to page NINDS - 35 of this document for the response to this significant item regarding epilepsy.

Item

Fragile X - The Committee urges the NINDS to intensify its research into these issues as they relate to Fragile X, and to coordinate this research with other Institutes working on Fragile X, including but not limited to NIMH and NICHD. (p 112)

Action taken or to be taken

Please refer to page NINDS - 49 of this document for the response to this significant item regarding Fragile X.

Item

FXTAS - FXTAS is a newly discovered, progressive neurological disorder that affects older men who are carriers of a premutation in the same gene that causes Fragile X syndrome. Identification of older male carriers will lead to a better understanding of the true incidence of Fragile X syndrome and afford at-risk families of child-bearing age the opportunity to pursue genetic counseling. NINDS, in collaboration with the National Institute on Aging, is urged to commit additional resources and expand research into FXTAS, including working with the other NIH institutes as well as the Centers for Disease Control and Prevention in the development of genetic counseling protocols for families affected by both Fragile X and FXTAS. (p. 112-113)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports a variety of investigator-initiated research projects on Fragile X syndrome and on Fragile X-associated Tremor/Ataxia Syndrome (FXTAS). Fragile X syndrome is caused by a gene mutation, called a repeat expansion mutation, which adds a long stretch of abnormal DNA to the genetic sequence. If the repeat expansion is long enough to cause a complete loss of function in the gene product - the Fragile X Mental Retardation Protein (FMRP) - Fragile X syndrome results. In the case of FXTAS, the repeat expansion is called a premutation because is not quite long enough to cause Fragile X syndrome. However, late-onset motor abnormalities and cognitive decline in a subgroup of older men who carry the Fragile X premutation suggest that even the smaller repeat expansion alters the function of the FMRP protein and causes neurological symptoms. More recently, a milder form of the syndrome has also been found in female premutation carriers. Investigators supported by the NINDS and the National Institute for Child Health and Human Development (NICHD) have suggested new guidelines to facilitate proper diagnosis of FXTAS, which should improve estimates of the incidence of the disease and facilitate genetic counseling.

The NINDS continues to support a number of basic research studies into the function of the normal and pathological FMRP protein in order to provide a foundation for translational and clinical research on effective treatment strategies for FXTAS. Two clinical research projects funded by the NINDS are focused on identifying the neurological alterations in carriers of the premutation associated with FXTAS. Together, these studies will provide information about the clinical features of this newly-recognized disorder, including the rate of progression, and the relationship between the gene abnormality and the severity of FXTAS symptoms.

Both the NINDS and the National Institute on Aging participate in the "Ethical, Legal, Social Issues Regular Research Program," (PA-04-050) led by the National Human Genome Research Institute, to solicit studies on implications of research, technologies, and information related to genetic disorders. The announcement encourages investigators to submit research proposals on genetic conditions, including Fragile X and FXTAS, and on related clinical issues like genetic counseling. The NINDS considers proposals to develop genetic counseling protocols for Fragile X and FXTAS to be responsive to this announcement, and encourages investigators interested in this topic to apply for funding.

Item

Learning disabilities - The Committee commends NINDS for the work conducted to explore the neurological aspects of learning disabilities. The Committee looks forward to learning the results of this work and encourages the Institute to continue to coordinate with other Institutes working on related activities. (p.113)

Action taken or to be taken

Learning disabilities affect the ability to understand or use spoken or written language, do mathematical calculations, coordinate movements, or direct attention; they may be the result of defects in neurological development that result in neurobehavioral deficits. The National

Institute of Neurological Disorders and Stroke (NINDS) supports a varied portfolio of studies of neurological disorders which result in cognitive deficits and learning disabilities, including fragile X syndrome, attention deficit disorder, Down syndrome, dyslexia, autism, and tuberous sclerosis. The studies measure a range of biological factors related to learning disabilities. For instance, the NINDS continues to fund the Center for the Neural Basis of Language and Learning, a multi-disciplinary center at the University of California, San Diego. This multi-disciplinary center explores the neural bases of language and learning in children who are at risk for communication disorders by combining behavioral and neural imaging techniques to study normal and abnormal brain development. Other NINDS-funded studies are investigating neurocognitive development in boys diagnosed with Duchenne muscular dystrophy and fragile X, in order to better characterize the neuropsychological development of these patients and to understand the genetic basis of the various elements of cognitive impairment. Another NINDS-funded study is focused on identifying genes that correlate with a susceptibility to dyslexia and developmental language disorders; this may shed light on the molecular mechanisms underlying these disorders. Other NINDS-funded researchers are investigating whether dyslexic and normal volunteers differ in the brain areas that are active during reading tasks that are typically difficult for dyslexics. The results are expected to help guide the development of improved methods of diagnosis, rehabilitation, and treatment of dyslexia.

The NINDS has participated and will continue to partner with other NIH Institutes and Centers at NIH on initiatives, workshops and other activities relevant to learning disabilities. For instance, the NINDS, the National Institute of Mental Health (NIMH) and the National Institute of Child Health and Human Development (NICHD), together with two patient advocacy groups, co-sponsor a Program Announcement (PA) with set-aside funds to encourage basic and clinical research on Rett Syndrome. The NINDS is also collaborating with the National Institute on Aging (NIA), the National Institute of Drug Abuse, and the National Institute of Environmental Health Sciences on a PA to promote the identification of susceptibility genes for complex neurological and neurobehavioral disorders, including disorders that involve learning disabilities and cognitive deficits. Finally, in 2005, NINDS together with NICHD, NIMH, and NIA held a workshop entitled “Down syndrome: toward optimal synaptic function and cognition.” Down syndrome (DS) is the most common genetic cause of mental retardation. The workshop was held to discuss the neuronal signaling (synaptic) processes that underlie the cognitive deficits of DS and to identify research priorities critical for the development of therapies.

Item

Mucopolysaccharidosis (MPS) - The Committee commends NINDS efforts to collaborate with the Lysosomal Storage Disorder Research Consortium [LSDRC] in the development and release of the July 2004 program announcement titled ‘CNS Therapy Development for Lysosomal Storage Disorders’ and the stated intent to enhance blood brain barrier research in lysosomal storage disorders. The Committee continues to encourage NINDS to collaborate with all appropriate Institutes and Centers to support ongoing MPS research, including study of the blood brain barrier as an impediment to treatment, and use all available mechanisms to further stimulate and enhance efforts to better understand and treat MPS disorders (p. 113)

Action taken or to be taken

Please refer to page NINDS - 49 of this document for the response to this significant item regarding MPS.

Item

Neurofibromatosis - The Committee encourages NINDS to aggressively expand its NF clinical and basic research portfolios. The Committee commends NINDS for its leadership role in NF research and in coordinating efforts with other Institutes engaged in NF research. The Committee recognizes that basic research has now successfully brought NF research into the clinical era. The Committee therefore encourages NINDS to continue its exemplary efforts in the creation, implementation, and funding of NF clinical trials infrastructures and clinical trials using existing and new drugs on NF patients. The Committee calls upon NINDS to continue to coordinate its efforts with the other institutes at NIH as well as other government agencies. (p.113)

Action taken or to be taken

Please refer to page NINDS - 46 of this document for the response to this significant item regarding neurofibromatosis.

Item

Neuroprosthetics - The Committee strongly supports research on neuroprosthetics, such as the Brain Machine Interface (or Human Assisted Neurological Device) project. This research offers great promise in restoring movement in individuals suffering from a variety of neurological disorders, including paralysis, stroke and wound-related trauma, and should be expanded. (p.113)

Action taken or to be taken

More than 35 years ago, the NINDS Neural Prosthesis Program set a goal of developing devices to restore or replace lost functions in people with neurological impairments. Since then, the program has been a major catalyst of research on neuroprostheses. This includes the development of brain machine interfaces that monitor movement control signals directly from the brain. The Institute supports the development of devices that rely upon the weak brain wave signals that can be detected with scalp electrodes and of those that use chronically implanted electrodes to record the activity of multiple individual nerve cells in movement control areas of the brain. The highly interdisciplinary Neural Prosthesis Program supports biomaterials scientists who work with experts in brain tissue to develop implantable electrodes that can reliably perform in the brain for months at a time without doing harm. Experts in micro-fabrication techniques design tiny implantable multi-electrode arrays that detect signals from many neurons simultaneously. Electronics and computational scientists and engineers develop

methods to rapidly extract useful information from implanted electrodes or from complex and faint signals detected non-invasively from the surface of the scalp. Over the years, research teams supported by the program have contributed to the development of cochlear prostheses for hearing impaired people, nerve and muscle stimulation for bowel and bladder control, respiratory control, grasping, standing and walking, as well as pioneering efforts in brain machine interfaces.

As the NINDS continues the Neural Prosthesis Program, the Institute works closely with other components of NIH that now share an interest in this promising area of research.
The National Institute of Biomedical Imaging and Bioengineering (NIBIB) promotes technology development in this area. The National Institute on Deafness and Other Communications Disorders (NIDCD) focuses on auditory neuroprostheses. The National Center for Medical Rehabilitation (NCMRR) Research, within the National Institute of Child Health and Human Development (NICHD), has an interest in applications to rehabilitation. The NIH investments in nanotechnology, computational science, and interdisciplinary studies, through the Roadmap and other programs, are also directly relevant. As the field has progressed, the Department of Defense has begun a major program to produce a next generation of BCI-based prosthetic limbs to meet the needs of soldiers who have experienced amputation.

Item

PET Imaging and Alzheimer's Disease -- The Committee urges the NINDS, in collaboration with the NIA and NIMH, to expand its research into early diagnosis of Alzheimer's using PET imaging of the brain, and to share its results with the Centers for Medicare and Medicaid Services. (p. 113)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA) continue to support imaging studies that might provide earlier diagnosis of Alzheimer's disease (AD), and potentially permit earlier intervention. For example, both Institutes are funding researchers currently exploring the use of positron emission tomography (PET) and functional magnetic resonance imaging (MRI) to examine plaques and tangles, the cellular hallmarks of AD, in individuals with a genetic predisposition to the disorder. In addition, recently-published results from one group of NINDS-funded investigators suggest that PET – particularly multiple PET measures – may be useful in helping clinicians establish an accurate diagnosis of AD or another form of dementia in symptomatic individuals. Recent results from a group of NIA-funded investigators support the concept that an accurate, reliable and possibly specific clinical diagnosis of AD in the early, mild cognitive impairment (MCI) stage is a reasonable expectation using brain imaging and other tests. In some cases, neuroimaging in combination with neuropsychometrics may be superior to using neuropsychological testing alone. As advances in early diagnosis are made, it may be critical to ensure that these diagnoses are as accurate as possible, since therapeutic indications may differ for different forms of dementia.

In addition to these efforts, the NIA has recently initiated the Alzheimer's Disease Neuroimaging Initiative (ADNI), a five-year, public-private partnership designed to improve the ability of

imaging techniques, including PET, and biological markers from blood and cerebrospinal fluid, to assess the progression of the early stages of AD. The NINDS will also work with the NIA and the National Institute of Mental Health to explore opportunities to encourage investigator-initiated applications for novel use or development of imaging techniques aimed at early diagnosis. The results of any such studies or those described above would be published in a peer-reviewed medical journal and available to the Centers for Medicare and Medicaid Services.

Item

Parkinson's Disease -- The Committee supports the innovative multidisciplinary research and training concerning Parkinson's disease provided by the Morris K. Udall Parkinson's Disease Research Centers of Excellence. The Committee urges NINDS to continue support for the Udall Centers. The Committee further encourages the Director to create an additional Coordinating Udall Center to further focus and manage the interdisciplinary efforts of the Udall Centers. The additional research opportunities and discoveries made by Udall Center scientists are leading to improved diagnosis and treatment of patients with Parkinson's. The Committee commends both the basic and clinical objectives of the Centers that, together, enhance research effectiveness in a multidisciplinary setting.

The Committee commends the NINDS for participating in a community-wide examination of private and public Parkinson's disease research funding through the Parkinson's Community Research Advisory Council. The Committee strongly encourages NINDS to continue to participate in this effort.

The Committee commends the Director for implementing the Neuroscience Blueprint, which creates new opportunities for collaborative, directed research across institutes and through public-private partnerships. As the NINDS develops Blueprint initiatives for this and future years, the Committee encourages continued collaborations including additional intramural activities between NINDS, NIMH, and NIA to enhance understanding of neurodegenerative diseases, particularly Parkinson's disease. Specifically, the Committee encourages collaborations with other institutes in the areas of genetics, cell biology, pathology/epidemiology, non-human models, biomarkers, neuroimaging, gene therapy, surgical approaches, drug development, cell replacement therapy (i.e., stem cells), and mental health which will lead to better treatments or a cure for this devastating and costly disease. In particular, the Committee urges continued research on biomarkers, for early detection of Parkinson's, and neuroprotective compounds, to slow or stop the disease until cures can be found. As the results of neuroprotection trials become known, the Committee urges the Director to provide funding for Phase III clinical trials of all the neuroprotection compounds found to be effective, including combinations of them. As Parkinson's is affecting men and women at progressively younger ages, causing many to have to stop working within a few years of their diagnosis, early diagnosis and identification of neuroprotective compounds are critical. (p. 113-114)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) plans to continue its Morris K. Udall Centers for Parkinson's Disease (PD) Research program, and is eager to

improve the coordination of research efforts across Centers. In a major step toward this goal, the Institute funded a PD Data Organizing Center (PD-DOC) in September 2004 to streamline the collection and distribution of clinical data across all the Udall and other PD research centers. PD-DOC will make a substantial contribution to the coordination of the research being undertaken by the Centers, particularly the clinical research projects. Udall Center directors and staff also meet annually to discuss results and coordinate their efforts. Regarding the need for additional coordination, the NINDS is currently sponsoring a formal evaluation of the Udall centers program which will provide valuable insights into the productivity of each Center in forming collaborations with investigators at other Centers. Subsequently, NINDS can utilize these data to determine if further coordination efforts are warranted.

Please refer to page NINDS -37 of this document for the response to this significant item regarding the NINDS involvement in the Parkinson's Community Research Advisory Council, the activities being undertaken as part of the Neuroscience Blueprint, and collaborative extramural projects across the NIH. With regard to intramural collaborations, NINDS investigators have developed a highly productive collaboration with intramural researchers at the National Institute on Aging, and the National Human Genome Research Institute, to explore the genetic causes of PD. These collaborations have produced several significant findings, including the discovery that a triplication of the alpha-synuclein gene can contribute to PD and the subsequent determination that this extra “dose” of alpha-synuclein is not a common cause of either sporadic or inherited PD.

NINDS recognizes that the development of biomarkers is one of the most significant challenges facing the PD research community. As a first step to explore the use of imaging tools as biomarkers, NINDS sponsored a workshop on this topic in July 2003. NINDS staff and the workshop participants subsequently published a 2005 paper in *Neurology* which outlines recommendations on methodological changes in studies to determine how imaging measures relate to clinical endpoints, and the development of new markers to better capture the degenerative process and more of the clinical features of PD.

NINDS also appreciates the tremendous potential impact of a positive finding in its Neuroprotection Exploratory Trials in PD (NET-PD) trials and the investigators are moving forward quickly with the analysis of the remaining data from the first four Phase II trials. An oversight board, which includes representatives from U.S. Food and Drug Administration and the PD patient community in addition to NINDS staff, is already involved in assessing the progress and available outcomes of each trial, and in planning possible next steps so that no time is wasted as the Phase II trials are completed and a decision is made regarding initiation of a Phase III trial.

Item

Peripheral Neuropathy -As many as 20 million Americans suffer from peripheral neuropathy, a neurological disorder that causes debilitating pain, weakness in the arms and legs, and difficulty walking. Peripheral neuropathy affects approximately one-third of diabetics, or about 5.1 million persons, while other forms of neuropathy are inherited; associated with cancer, kidney disease or infections like hepatitis, HIV/AIDS or Lyme disease; or caused by autoimmunity, traumatic

injuries, poor nutrition, toxins and certain medications. While significant research is underway on diabetic neuropathy and HIV/AIDS-related neuropathy, the Committee strongly urges NINDS to strengthen its research portfolio on other forms of neuropathy. The Committee is pleased to learn that NINDS plans to convene a workshop with distinguished scientists to identify research goals aimed at expanding the research knowledge base and identifying potential therapies. (p. 114)

Action taken or to be taken

Please refer to page NINDS - 39 of this document for the response to this significant item regarding peripheral neuropathy.

Item

Pick's Disease - The Committee urges the NINDS to initiate funding for drug discovery efforts that focus on specific targets relevant to treating the mechanisms underlying brain degeneration due to frontotemporal dementia [FTD]. The Committee further encourages the NINDS to conduct multicenter treatment trials for symptomatic management of Pick's disease and other FTDs. The Committee encourages the Institute to focus on methods for discovering the causes of this family of diseases, improving diagnostic accuracy, and providing longitudinal characterizations so that the success of intervention can be determined. (p. 114)

Action taken or to be taken

Please refer to page NINDS - 51 of this document for the NINDS response to this significant item regarding Frontotemporal Dementia/Pick's Disease.

Item

Rett Syndrome - The Committee remains concerned at the level of funding dedicated toward research into the genetic cause of Rett syndrome, an incurable childhood neurological disorder that is the leading cause of severe neurologic impairment in females and the only autism spectrum disorder that is known to have a genetic cause. While once considered rare, increased diagnosis suggests that the prevalence of Rett syndrome may be much greater than the current estimated incidence of 1 in every 10,000 females. The discovery of the specific genetic cause of Rett syndrome could help elucidate a host of other disorders, including autism, schizophrenia, Parkinson's, anxiety, and autonomic nervous system disorders. Accordingly, the Committee strongly urges NIH to dedicate enhanced resources to research on the genetic cause of Rett syndrome. The Committee also encourages NIH to coordinate with private organizations supporting research initiatives in this area in order to ensure the most efficient use of resources (p.115)

Action taken or to be taken

The NIH is committed to working toward a cure for Rett syndrome. The National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH),

National Institute of Child Health and Human Development (NICHD), National Center for Research Resources (NCRR), and National Institute of General Medical Sciences (NIGMS) support Rett research, and NIH funding has enabled several important advances toward understanding the molecular basis of Rett. In 1999, NIH-supported researchers discovered that Rett syndrome results from mutations in methyl-CpG-binding protein 2 (MeCP2), a regulator of gene expression. More recently, scientists have gathered clues to how MeCP2 affects the nervous system. Researchers co-funded by the NIH, International Rett Syndrome Association (IRSA), and Rett Syndrome Research Foundation (RSRF) found that MeCP2 regulates genes responsible for neurotransmitter production and brain patterning during embryonic development. Other researchers, funded by NIH, RSRF, and Cure Autism Now discovered that MeCP2 interacts with YB-1, a protein that helps process several gene products important for nervous system function and development. Interestingly, YB-1 also interacts with another protein, FMRP, which is defective in Fragile X patients. This connection suggests a molecular basis for the similarities in Fragile X and Rett symptoms.

Current NIH research grants support further investigations into the molecular basis of Rett. Several NINDS projects are examining how MeCP2 mutations affect gene expression in cell and animal models. One NINDS-funded research team is exploring whether Rett mutations affect the ability of MeCP2 to respond to certain cellular signals. Another is studying the connections between MeCP2 mutations and cognitive and motor problems associated with Rett.

In general, the level of funding for Rett is based on the number of high quality grant applications submitted by the research community. The NINDS, NIMH, and NICHD recently partnered with the IRSA and RSRF to enhance research on Rett and MeCP2 via a Program Announcement with set-aside funds. This solicitation encourages applications for developmental, neuroanatomical, molecular genetic, and pathophysiological research; therapy development projects; and clinical studies. Released in November 2004, the solicitation will remain active for three years. The NIH anticipates making its first round of awards in FY 2006.

Item

Tuberous Sclerosis Complex (TSC) - Tuberous sclerosis complex, or TSC, is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body, including the brain, heart, kidneys, liver, eyes, and/or skin. Individuals with TSC—many of whom are infants and young children—face a lifetime of suffering with kidney failure, seizures, behavioral disorders, autism, and mental retardation. The Committee is encouraged that NINDS has organized a Trans-NIH Tuberous Sclerosis Coordinating Committee, and urges NINDS to continue to take a leadership role in convening meetings of this Committee, facilitating communication between the participating institutes, and encouraging the funding of TSC-related research. The Committee also encourages NINDS to host a pre-clinical translational research workshop on TSC and to include TSC in the NINDS Pilot Therapeutic Network [NPTUNE] (p. 116)

Action taken or to be taken

The NINDS convened a meeting of the Trans-NIH Tuberous Sclerosis Coordinating Committee in August, 2005, which included representatives from the National Cancer Institute (NCI),

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of General Medical Sciences (NIGMS), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Mental Health (NIMH), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Child Health and Human Development (NICHD), Office of Rare Diseases (ORD), Tuberous Sclerosis Alliance (TSA), and Department of Defense Congressionally Mandated Research Program for TSC. The meeting participants reviewed their current research portfolios and discussed potential partnerships to promote TSC research. The NINDS, NIDDK, NIMH, NIAMS, NCI, and TSA have already collaborated in supporting an FY06 Program Announcement aimed at understanding or treating TSC. The first round of applications will be considered for funding in September, 2005.

The NINDS supports several mechanisms to encourage therapy development for neurological diseases. The NINDS Pilot Therapeutic Network (NPTUNE) is a relatively new initiative. To ensure that potential treatments for neurological diseases are tested in pilot clinical trials in a timely and efficient way, NINDS has awarded a contract to establish a standing network of sites under a single operations center that can implement small scale trials for different neurological diseases. The trials conducted by this network will be studies to gain information about a potential intervention (such as the dose, safety, and preliminary evidence of activity) needed to design a phase III trial. The NINDS anticipates supporting one or two studies per year; the Institute has developed a rigorous and transparent process and criteria for selecting diseases and interventions for use in NPTUNE and will consider TSC under this process. Investigators are also invited to submit proposals for TSC clinical trials through the regular grant application process. The NINDS will consider a workshop on therapy development for TSC as yet another way of stimulating progress in this area.

Item

Vulvodynia- The recently published findings of NIH-supported research indicates that millions of women suffer from chronic pelvic and genitourinary pain conditions such as vulvodynia. Therefore, the Committee calls on NINDS to expand its support of research in this area, in coordination with NICHD, ORWH, the NIH Pain Consortium and other ICs, with a focus on etiology and multi-center therapeutic trials. (p.116)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports a wide portfolio of studies on the neurological basis of pain and pain disorders; studies on visceral and gynecological pain have particular relevance to vulvodynia. For example, NINDS-funded researchers are characterizing the connections neurons make with female reproductive organs and examining the mechanisms underlying gynecological pain. Several studies are also focusing on understanding biochemical and functional differences between nerves which respond to pain in the skin and those which convey pain from internal organs. Results from these studies will improve our understanding of visceral and gynecological pain and may be relevant to the study and treatment of vulvodynia.

The NINDS has collaborated and will continue to partner with other Institutes and Centers at NIH on initiatives and other activities relevant to pain research. For example, NINDS sponsors, along with the National Institute of Child Health and Human Development (NICHD), the National Institute of Nursing Research (NINR), the National Institute of Dental and Craniofacial Research (NIDCR) and six other institutes, a program announcement entitled "Biobehavioral Pain Research" to encourage research aimed at studying the individual experience of pain in all types of pain conditions, and examining the pain experience from a basic, clinical, and biopsychosocial research perspective. In addition, the Director of NINDS co-chairs the NIH Pain Consortium, together with the Directors of NINR and NIDCR. The NIH Pain Consortium is an inter-NIH group that meets regularly to enhance pain research. The Pain Consortium fosters coordination and collaboration among the many NIH Institutes and Centers that have programs and activities addressing pain. One of the recent activities of the Pain Consortium was the development of a website (http://painconsortium.nih.gov/) to increase visibility for pain research - both within the NIH intramural and extramural communities, as well as outside the NIH.

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2006 Amount Authorized	FY 2006 Appropriation	2007 Amount Authorized	FY 2007 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$1,501,850,000	Indefinite	$1,492,007,000
Disorders and Stroke	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	32,907,000		32,743,000
Total, Budget Authority				1,534,757,000		1,524,750,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1998	722,712,000 2/	763,325,000	781,351,000	(780,713,000)
1999	815,649,000 2/3/	851,066,000	903,278,000	903,278,000
Rescission				(598,000)
2000	890,816,000 2/	979,281,000	1,019,271,000	1,034,886,000
Rescission				(5,510,000)
2001	1,050,412,000 2/	1,185,767,000	1,189,425,000	1,176,482,000
Rescission				(383,000)
2002	1,316,448,000	1,306,321,000	1,352,055,000	1,328,188,000
Rescission				(1,522,000)
2003	1,432,305,000	1,432,305,000	1,466,005,000	1,466,005,000
Rescission				(9,529,000)
2004	1,468,926,000	1,468,326,000	1,510,926,000	1,510,776,000
Rescission				(9,569,000)
2005	1,545,623,000	1,545,623,000	1,569,100,000	1,539,448,000
Rescission				(12,675,000)
2006	1,550,260,000	1,550,260,000	1,591,924,000	1,550,260,000
Rescission				(15,503,000)
2007	1,524,750,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research
3/ Reflects a decrease of $2,457,000 for the budget amendment for Bioterrorism

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Office of the Director	53	56	56
Division of Intramural Research	385	393	396
Division of Extramural Activities	93	100	100
Total	531	549	552
Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research			
FTEs supported by funds from Cooperative Research and Development Agreements	(2)	(2)	(2)

FISCAL YEAR	Average GM/GS Grade
2003	11.2
2004	11.2
2005	11.7
2006	11.7
2007	11.8

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Detail of Positions

GRADE	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Total - ES Positions	4	4	4
Total - ES Salary	$587,987	$608,611	$623,887
GM/GS-15	32	34	34
GM/GS-14	40	42	43
GM/GS-13	63	67	66
GS-12	58	61	61
GS-11	52	50	51
GS-10	6	6	6
GS-9	32	34	35
GS-8	14	15	15
GS-7	11	11	10
GS-6	6	6	5
GS-5	0	0	0
GS-4	1	1	1
GS-3	1	1	1
GS-2	0	0	0
GS-1	1	0	0
Subtotal	317	328	328
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade	4	4	4
Senior Grade	2	3	3
Full Grade	2	1	1
Senior Assistant Grade			
Assistant Grade			
Subtotal	8	8	8
Ungraded	201	210	213
Total permanent positions	348	359	359
Total positions, end of year	530	550	553
Total full-time equivalent (FTE) employment,end of year	531	549	552
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$146,997	$152,153	$155,972
Average GM/GS grade	11.7	11.7	11.8
Average GM/GS salary	$78,539	$81,294	$83,334

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

New Positions Requested

	FY 2007		
	Grade	Number	Annual Salary
Intramural Fellow		3	$70,000
Total Requested		3	