# FISCAL YEAR 2004

Justification of Appropriation

Estimates

National Institutes of Health

**National Institute of Neurological Disorders and Stroke**

February 4, 2003

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke


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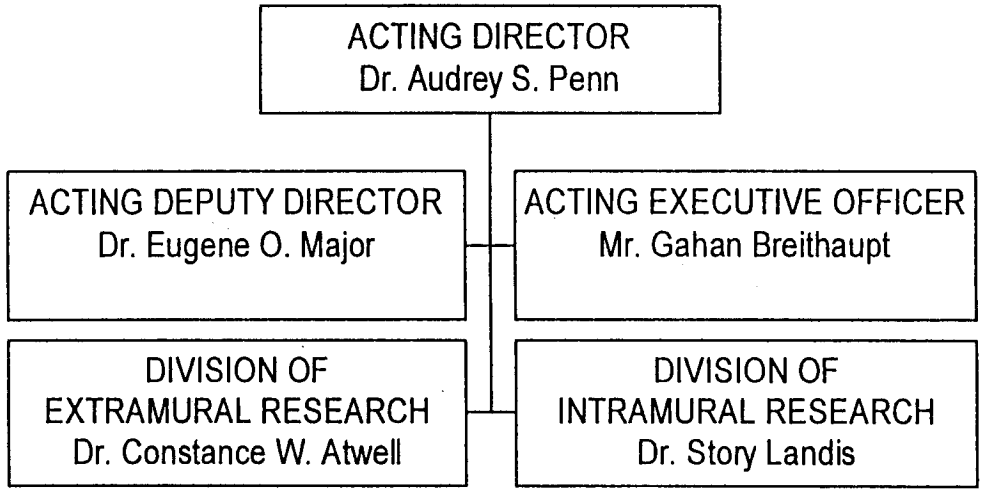
NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Organizational Structure



## 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, $1,468,926,000.*

**National Institutes of Health**
**National Institute of Neurological Disorders and Stroke**

**Amounts Available for Obligation 1/**

| Source of Funding | FY 2002 Actual | FY 2003 Amended President's Budget | FY 2004 Estimate |
|---|---|---|---|
| Appropriation | $1,328,188,000 | $1,432,305,000 | $1,468,926,000 |
| Enacted Rescissions | (1,522,000) | (0) | --- |
| Subtotal, Adjusted Appropriation | 1,326,666,000 | 1,432,305,000 | 1,468,926,000 |
| Real transfer to: Other HHS Agencies through Secretary's one-percent transfer authority | (1,434,000) | (0) | (0) |
| Comparative transfer from: Fogarty International Center for International Services Branch | 68,000 | 68,000 | 0 |
| Comparative transfer to: Office of the Director for program changes | (882,000) | (952,000) | (0) |
| National Institute of Biomedical Imaging and Bioengineering | (15,000,000) | (15,000,000) | (0) |
| Subtotal, adjusted budget authority | 1,309,418,000 | 1,416,421,000 | 1,468,926,000 |
| Unobligated Balance, start of year | 0 | 0 | 0 |
| Unobligated Balance, end of year | 0 | 0 | 0 |
| Subtotal, adjusted budget authority | 1,309,418,000 | 1,416,421,000 | 1,468,926,000 |
| Unobligated balance lapsing | (39,000) | --- | --- |
| Total obligations | 1,309,379,000 | 1,416,421,000 | 1,468,926,000 |

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2002 - $8,156,000 FY 2003 - $9,000,000 FY 2004 - $9,000,000
Excludes $113,460 in FY 2002 and $200,000 in FY 2003 for royalties.

Justification

National Institute of Neurological Disorders and Stroke

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Authorizing Legislation:Section 301 of the Public Health Service Act, as amended
Reauthorizing legislation will be submitted.

Budget Authority:

| FY 2002 Actual | | FY 2003 Amended President's Budget | | FY 2004 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|---|
| FTEs | BA | FTEs | BA | FTEs | BA | FTEs | BA |
| 605 | $1,309,418,000 | 609 | $1,416,421,000 | 599 | $1,468,926,000 | (10) | $52,505,000 |

This document provides justification for the Fiscal Year 2004 activities of the National Institute of Neurological Disorders and Stroke (NINDS), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2004 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR).

**Introduction**

*The Mission:* The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disorders by finding ways to prevent, to treat, and ultimately, to cure these diseases. The diverse needs of neurological disorders are especially suited to the NIH system for fostering high quality scientific research, and to carry out its mission, NINDS supports a wide spectrum of research. Fundamental studies of the normal and diseased nervous system, from the molecular to the behavioral level, continue to generate new therapeutic and prevention strategies. Translational studies bring findings from laboratory studies to readiness for testing in clinical trials, and insights from the clinic back to the lab. Clinical trials evaluate the safety and effectiveness of interventions to prevent or treat disease. The Institute is actively engaged at all of these levels. In addition, public education efforts to relay scientific findings that can affect the public health are increasingly critical to the Institute's mission, as we learn more about preventing and treating neurological disorders.

*The NINDS extramural research program*, which accounts for the majority of the research supported by the Institute, relies heavily upon the wisdom and ingenuity of the extramural research community - scientists and physicians throughout the nation who monitor research priorities, participate in NINDS strategic planning efforts, seek out scientific opportunities, propose new research projects, evaluate proposals, carry out research, and train the next generation of researchers.

The Institute also relies on the wisdom of its own scientific program staff in the Division of Extramural Research to plan and implement research agendas for neurological disorders. In recent years, motivated by public health needs, responding to rapidly changing science, and empowered by generous funding increases, the Institute has increasingly accepted the challenge of more actively stimulating the interests of the scientific community in particular areas of research. This activism is guided by extensive and inclusive strategic planning efforts and by consultation with the National Advisory Neurological Disorders and Stroke (NANDS) Council. Implementation occurs through sponsoring scientific workshops, promoting special consideration of applications critical to the Institute's mission, issuing grant and contract solicitations targeted to specific needs and opportunities, and developing programs designed to address special issues of research in areas such as clinical trials, translational research, and high impact science. The Institute also has extensive programs for the training of basic and clinical investigators. Increasingly, many aspects of NINDS activities involve public-private partnerships.

*The NINDS intramural research program,* which accounts for approximately 10 percent of the Institute's budget, is one of the largest neuroscience research centers in the world, with a distinguished history of accomplishment. Investigators in the NINDS intramural program conduct research in the basic, translational, and clinical neurosciences. Their specific interests cover a broad range of neuroscience research including molecular biophysics, synapses and circuits, neuronal development, integrative neuroscience, brain imaging and neurological disorders. Through collaboration, pre- and postdoctoral training programs, jointly sponsored seminar series and special interest groups, NINDS investigators and investigators in other intramural programs (NIMH, NEI, NIDCD and NICHD) contribute to a vital and growing neuroscience research community at the National Institutes of Health.

While continuing to build on its individual strengths, the program is also responding to the changing landscape of science. Now, more than ever, disparate scientific and medical disciplines must come together to expedite progress against neurological diseases. To this end, NINDS, together with NIMH, led concept development and planning for the NIH John Edward Porter National Neuroscience Center. The first stage of construction, to replace a neuroscience research building on the NIH Bethesda campus, has begun and is scheduled to open in FY 2007. The overarching vision is to "put the brain back together" by overcoming artificial disciplinary boundaries within and across institutes and by setting the standard for collaborative research in neuroscience.

*The Burden:* The burden of neurological disorders is immense, affecting all segments of society. Diseases of the nervous system kill people of all ages, disrupt essential bodily functions, cause pain and discomfort, and disturb all aspects of human ability, from perception and movement through emotions, memory, language, and thinking.

Some neurological disorders are among the most common of all human afflictions[1]. Stroke is the third leading cause of death in the United States and a major cause of disability. More than 5.3

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[1]Note: Burden of illness figures in this document are from *Disease-specific Estimates of Direct and Indirect Costs of Illness and NIH Support, 2000*, DHHS, and *Progress and Promise, 1992*, Report of the National Advisory Neurological Disorders and Stroke Council.

million Americans experience disabilities resulting from traumatic brain injury, in addition to more than 50,000 who die each year. Alzheimer's, Parkinson's and other neurodegenerative diseases are increasingly a problem as our population ages. Epilepsy and other seizure disorders may affect as many as one percent of all Americans. Pain is the most common reason people seek medical care. There are hundreds of less common or rare nervous system disorders. A sampling of these includes amyotrophic lateral sclerosis (Lou Gehrig's disease), ataxias, autism, Batten disease, Canavan disease, cerebral palsy, Creutzfeld-Jakob disease, dysautonomias, dystonias, encephalitis, Huntington's disease, leukodystrophies, Lewy body dementia, meningitis, muscular dystrophies, multiple sclerosis, multiple system atrophy, myasthenia gravis, Parkinson's disease, peripheral neuropathies, progressive supranuclear palsy, restless legs syndrome, Rett syndrome, spina bifida, spinal cord injury, stiff person syndrome, syringomyelia, Tay-Sachs disease, and tuberous sclerosis. Together diseases of the nervous system, common and rare, have an enormous impact.

*The Challenge:* Diseases of the nervous system have always challenged medicine, often defying the best efforts at treatment and prevention. Neurological disorders can affect all parts of the nervous system, including the brain, spinal cord, and nerves of the body, as well as muscles and their control. Many causes are responsible. Trauma, infections, toxic exposure, degenerative diseases, tumors, gene mutations, systemic illness, vascular events, nutritional deficiencies, and adverse effects of essential treatments for other diseases can disrupt the functions of the nervous system. Compounding the challenge of confronting these diseases, the brain and spinal cord are difficult to access, sensitive to intervention, reluctant to regenerate following damage, intricate in structure, and elusive in their normal workings.

*The Progress:* Despite the challenges, progress in treating and preventing neurological disorders is gathering momentum. The first treatments—albeit still far from adequate— have proven effective for reducing damage from stroke and spinal cord injury. Immune therapies now reduce symptoms and slow the progression of multiple sclerosis. Surgical options have become available for treating Parkinson's disease and epilepsy. New drugs have emerged for headache and chronic pain conditions. Enzyme therapies have brought the first successes in treating Gaucher and Fabry disease and potentially other enzyme deficiency disorders. Molecular genetics and brain imaging are augmenting clinicians' insights to diagnose the bewildering array of diseases and to guide therapy. Advances in the prevention of neurological disorders are also notable. For example, this year alone almost a quarter of a million fewer deaths from stroke will occur than would have been expected without progress in prevention. Prevention of nervous system birth defects, such as spina bifida, and genetic counseling for inherited disorders, such as Tay-Sachs disease, are also having a major impact on public health.

*The Promise:* Although treatment and prevention of neurological diseases have been improving, for many of these disorders even the best available interventions are only partly effective in alleviating symptoms and fail to halt the progression of disease. However, an unprecedented variety of new treatment and prevention strategies are currently under development. These include drugs to home in on the molecules that cause disease, stem cell therapies to replace lost nerve cells, neural prostheses to read control signals directly from the brain, vaccines to prevent stroke, implantable devices to compensate for brain circuits unbalanced by disease, immune modulators to ameliorate autoimmune disorders, therapies to repair or replace defective genes,

and behavioral interventions to encourage the latent "plasticity" of the brain and spinal cord to repair themselves or reorganize to compensate for damage.

## SCIENCE ADVANCES: UNDERSTANDING THE NERVOUS SYSTEM IN HEALTH AND DISEASE

Progress in preventing and treating neurological disorders relies on understanding the normal workings of the nervous system and what goes wrong in disease. The emerging new modalities for combating disease highlight this: Stem cells and neurotrophic strategies arose from fundamental studies of nervous system development. Deep brain stimulation, which shows promise for Parkinson's, dystonia, and other diseases, relies upon research techniques developed to monitor the activity of single nerve cells in the brain, and on basic knowledge of anatomical circuits that control movement. Studies of how the brain learns are leading to therapies that may enhance "brain plasticity" to repair damage. Surprisingly, advances in understanding brain plasticity are also giving new insights into what causes chronic pain conditions, epilepsy, and perhaps focal dystonias. Gene therapy, new understanding of the molecular basis of diseases, diagnostic tests, and animal models for testing therapies are among the many fruits of fundamental studies in neurogenetics. The following are recent examples of scientific advances in understanding the healthy and diseased nervous system:

*Neuronal precursors respond to brain injury:* Over the last few years scientists have found that, even in the adult human, certain regions of the brain can give rise to new nerve cells. New studies in laboratory rats show that primitive neuronal precursor cells respond to experimentally induced strokes and epileptic seizures by multiplying, migrating to damaged brain areas, and forming new nerve cells appropriate to that area of the brain. Surprisingly, one study found that precursor cells may also migrate from bone marrow to brain, although their role is not yet clear. Finding the chemical signals that activate and control these self-repair responses may lead to new avenues for therapy, but much better understanding is necessary before human therapy can safely be attempted because there can be harmful consequences. Indeed, new cells in the brain's dentate gyrus may contribute to the over excitability of brain circuits that underlies epilepsy.

*Astrocytes instruct neural stem cells to become neurons:* To treat neurological disorders, we might someday direct neural stem cells in cell culture to form cell types needed for transplantation, or perhaps stimulate stem cells within the brain itself to form new cells to repair damage from disease or trauma. Either strategy depends on understanding the signals that control the proliferation and specialization of neural stem cells. New research shows that astrocytes, a type of supporting cell in the brain, can instruct neural stem cells to become neurons. These experiments provide an important step towards identifying the specific signals involved and learning how to control stem cells for therapeutic applications.

*Links between adult brain stem cells and malignant gliomas:* Malignant gliomas are the most common primary brain tumors and among the most difficult of all cancers to treat. Extensive laboratory studies of malignant gliomas that were surgically removed from patients, then grown in cell culture, now suggest that cells derived from these tumors maintain stem cell-like

properties. If so, this could lead to new treatments--rather than attempting to kill tumor cells which escape radiation and surgery, we might redirect them to a more normal growth pattern.

*Autoimmune link in juvenile Batten disease:* For years, researchers have tried to determine how the defective gene in juvenile Batten disease leads to the seizures, mental impairment, and other symptoms of this devastating childhood disorder. A new study shows that mice engineered to lack the gene that is mutated in this disorder have an immune reaction that disables an important enzyme in the brain. The study also found signs of this reaction in children with Batten disease. This is the first study to show that autoimmunity might play a role in a pediatric neurodegenerative disorder of genetic origin and may suggest new approaches to treating the disorder.

*Understanding how inherited defects cause facioscapulohumeral muscular dystrophy:* Facioscapulohumeral muscular dystrophy (FSHD) is a degenerative disorder that causes muscle weakness and atrophy in the the face (facio), shoulders (scapulo), and upper arms (humeral). About 10 years ago, scientists found that nearly all people with FSHD are missing part of chromosome 4, but the chromosome defect does not appear to delete or directly disrupt a gene, so how these alterations result in the disease has been a mystery. In a new study, researchers show that the deletion in people with this disorder allows nearby genes on the chromosome to go into overdrive. This presents a major advance in understanding a common form of muscular dystrophy. Determining which gene(s), through over-expression, cause muscle to degenerate is an obvious avenue for further research that may lead to strategies for treatment.

*Microarray analysis yields new targets for drugs in multiple sclerosis:* Using microarray analysis, a team of researchers has advanced our understanding of what goes wrong in multiple sclerosis and identified new targets for drugs to combat the disease. Microarrays allow scientists to study the activity of thousands of genes at once, giving an unprecedented window on cellular functions. Researchers compared the activity of genes in autopsy samples of acute multiple sclerosis brain lesions, in chronic "silent" lesions without inflammation which produce no overt symptoms, and in normal brain tissue. The activity of several genes differed significantly between the active and silent lesions, as well as between diseased and normal brains, providing new insights into the underlying biology. Guided by the microarray results, scientists were able to reduce the symptoms in an animal model of multiple sclerosis by manipulating one gene in a genetically engineered strain of mice or by treating mice with the protein product of another gene, strengthening the evidence that the microarray finding may be important.

*Watching nerve cells and molecules in living animals:* The nervous system undergoes remarkable changes during development. In adults, changes continue, both in the normal course of life and in response to injury or disease. Until recently, scientists have been able to study these dynamic processes only indirectly. Over the last several years innovations in microscopy, new cell and tissue dyes, and genetic engineering of markers have converged to enable researchers to study dynamic processes in the nervous system at the cellular and even the molecular level in living animals. In one recent investigation, for example, scientists relied upon strains of mice genetically engineered so that different subsets of nerve cells connecting to muscle fluoresced in

different colors. The researchers could observe in 3-dimensions as the intermingled early nerve connections from different cells matured into the more orderly adult pattern.

*Delivering therapy to the brain:*The blood-brain barrier (BBB) protects the brain from toxic substances, but also prevents most potentially therapeutic drugs from entering the brain. Tiny blood vessels that make up the BBB contain specific transport systems which latch onto the molecules that the brain needs from the general circulation and carry only those chemicals into the brain. Scientists have developed a "Trojan horse" strategy to deliver drugs across the BBB. The idea is to trick specific transport systems into carrying a drug into the brain. In one experiment, a "Trojan horse" version of basic fibroblast growth factor, a natural survival promoting molecule, was given to rats intravenously an hour after an experimental stroke. The area of damaged brain was reduced by 70 percent by this treatment.

*Regulation of brain size:* Humans are smarter than other animals largely because we have a greatly expanded cerebral cortex. Scientists have identified a gene, and its corresponding protein product, that helps control how long neural precursor cells keep dividing to generate more cells, and thus how large the cerebral cortex becomes. When researchers genetically engineered mice to have a more active version of this protein, called beta-catenin, the mice developed a dramatically larger cerebral cortex that became highly folded, much like the human cortex, to fit within the skull. The mice died soon after birth so it is not clear how the large brains might affect their behavior. The results have many potential implications for understanding normal brain development, evolution, disorders of brain development, the regulation of neural precursor cells, and, perhaps, cancer.

*Abnormal cerebellar signaling induces dystonia in mice:* Dystonia is a common neurological disorder characterized by involuntary muscle contractions that produce twisting, abnormal postures, or repetitive movements. Dystonia can be mild but is often painful and disabling. Scientists recently shed new light on the causes of dystonia by focusing on a brain structure called the cerebellum, which is involved in coordinating movement but has not previously been implicated in this disease. By injecting drugs directly into the cerebellum to distort its activity, researchers recreated dystonia in mice. The animals exhibited twisted and contorted postures reminiscent of humans with the disease. Further, when the investigators blocked the abnormal signals coming from the cerebellum, the dystonia was relieved.

*Genes and environment in Parkinson's disease:* Despite many years of intensive study we still do not know what triggers dopamine nerve cells to die in Parkinson's disease. The discovery that the toxin MPTP, present in some batches of illegal drugs, causes a disorder that closely resembles Parkinson's disease, and subsequently that the pesticide rotenone has a similar effect on rats, focused attention on possible environmental triggers. More recently, the finding that rare mutations in the gene alpha-synuclein can cause Parkinson's disease highlighted the potential involvement of genes. A new study is bringing these lines of research together. Mice genetically engineered to lack alpha-synuclein are resistant to the toxic effects of MPTP. Together with other recent findings, which indicate a possible role for synuclein in regulating dopamine release, an understanding of how the interaction of genes and environment may trigger common Parkinson's disease is beginning to emerge.

*Genes control age of onset of Parkinson's and Alzheimer's disease:* Genetic screens have focused mainly on identifying genes that cause a disease, or increase risk. However, identifying genes that influence the age of onset is also important. Understanding the regulation of onset might make it possible to delay the disease, perhaps even beyond a person's normal life span. For the first time, scientists have screened the whole genome in several hundred families for genes that control onset of Parkinson's and Alzheimer's disease. The results demonstrate that genes do contribute significantly to age of onset, and that finding these genes is possible. More generally, this is one example of how geneticists are confronting the complexities of common neurological disorders, in which combinations of genes may influence the risk, onset, and course of diseases.

*First magenetoencephalographic recordings of visual activity in the brain of human fetus:* For the first time, researchers, using a unique scanning device, have shown that they can detect fetal brain activity in response to flashes of light transmitted through the mother's abdomen. The technique, called magentoencephalography (MEG), uses extremely sensitive magnetic sensors called SQUIDs (superconducting quantum interference devices) in a system called SARA (SQUID array for reproductive assessment). The pregnant women simply leaned against a smooth surface, allowing the sensors to detect signals from the entire maternal abdomen. Light flashes were brief, contained no harmful ultraviolet radiation, and were less intense than sunlight on a bright day. With refinement, this technique may help physicians detect and prevent fetal brain damage resulting from maternal hypertension, diabetes, and other conditions.

## *SCIENCE ADVANCES: TREATING AND PREVENTING NEUROLOGICAL DISORDERS*

NINDS efforts to prevent and treat neurological disorders include strategies that rely upon drugs, surgery, gene therapy, vaccines, immune system modulators, behavior, diet, neuroprosthetic devices, and cell or tissue transplantation. Research ranges from early studies of experimental therapies in animal models or cell culture, through multi-center clinical trials. The following highlight some recent findings:

*Vaccine prevents stroke in rats:* A vaccine that interferes with inflammation inside blood vessels greatly reduces the frequency and severity of strokes in spontaneously hypertensive, genetically stroke-prone rats. The vaccine was administered in a nasal spray and designed to capitalize on increasing understanding of the role of inflammation in stroke. Planning is underway to test the vaccine approach for stroke prevention in humans.

*Anticholesterol drug helps treat multiple sclerosis-like disease in mice:* Statins are among the most commonly prescribed drugs because they lower cholesterol, but scientists have also noted that statins reduce inflammation. Because of the role of inflammation in multiple sclerosis, researchers gave a statin to mice in which a disease similar to multiple sclerosis had been induced. The drug reduced the progression of disabling effects of the disease or even reduced paralysis that had already developed in some mice. Although the results are encouraging, the mouse model is not a perfect predictor of whether treatments will work, or even be safe, in the human disease. Careful trials in people will be needed to determine whether statins should be used to treat multiple sclerosis.

*Estrogen does not prevent second strokes:* Observational studies have suggested that estrogen replacement therapy may reduce the risk of stroke and death in postmenopausal women. However, it was not clear whether the apparent benefits of estrogen among women in those studies were due to hormone therapy or to other factors. The first randomized, controlled clinical trial designed to test whether estrogen can prevent a second stroke in postmenopausal women has found that the hormone therapy did not reduce the likelihood of a stroke or death compared to a placebo. This adds to the accumulating evidence that will help guide individual women, particularly those with pre-existing cardiovascular disease, in deciding whether hormone treatment is, on balance, appropriate for them.

*Progress toward treatments for learning disability in neurofibromatosis:* Neurofibromatosis type 1 (NF1) is characterized by peripheral nerve tumors (neurofibromas) and a variety of other problems that can be severe enough to cause death. NF1 is also one of the most common disorders in which defects in a single gene can cause learning disabilities. Researchers studying learning disabilities associated with NF, have traced the problem to excessive activity of a crucial signaling molecule. They successfully reversed the disabilities in mice by giving them an experimental drug targeting this problem. The findings provide hope that these learning problems may one day be treatable in humans.

*Direct brain control of neuroprosthetic devices:* Decades ago, when scientists first recorded the activity of nerve cells in the brain that control movement, researchers speculated that these brain signals might someday be harnessed to directly control neuroprosthetic devices. Scientists have now devised a system that brings this goal much closer. They implanted electrodes in the brains of monkeys and developed a sophisticated computer program to interpret the recorded signals. With this system monkeys can quickly and accurately move a cursor on a computer screen by thought alone. This system worked essentially instantaneously, without requiring any special training, and allowed control in a virtual 3-dimensional world.

*Genetic analysis of childhood brain tumors:* The difficulties of confronting brain tumors are compounded by the large number of different types–more than 100–with different prognoses and responses to therapy. New studies show that "gene fingerprints" can help classify types of childhood brain tumors and guide treatment decisions. The research relied upon the insight that tumors arise when damage to a succession of genes, taken together, releases cells from the normal controls on growth. Microarray technology allowed scientists to monitor the activity of thousands of genes in samples taken from tumors and associate increases or decreases in gene activity with tumor characteristics. When doctors can identify patients at relatively low risk from their tumors, they may use less aggressive therapy, minimizing long term side effects such as learning disabilities. Genetic approaches to brain tumors are also helping identify those that might respond to particular treatments and providing avenues for developing new therapies.

*Inhibiting Herpes infection:* Herpes simplex type 1 (HSV-1) is a virus that attacks nerve cells. HSV-1 eye infections are very common, second only to trauma as a cause of blindness in the industrialized world and potentially leading to life-threatening encephalitis (inflammation of the brain). Currently, there is no commercially available vaccine to prevent HSV infection. Scientists have developed a method to inhibit HSV-1 infection by topically applying DNA encoding a natural anti-viral molecule called interferon to the cornea of mice. The cells of the

eye take up the DNA and transiently make interferon, avoiding the systemic effects of injecting interferon itself. If confirmed in people, these results present the possibility of a low cost, non-invasive treatment for HSV infection.

*Inosine treatment stimulates brain rewiring and recovery following stroke:* New studies demonstrate that the natural chemical inosine can stimulate nerve fiber growth and substantially improve recovery of brain function following experimental strokes in rats. Inosine is one of several substances released by brain cells following stroke. The brain does exhibit a limited capacity to rewire and thus compensate for damage following stroke. Inosine apparently acts by stimulating this capacity to make new connections that compensate for damage.

*Minocycline delays onset and slows progression of ALS in mice:* Although most cases of ALS are not inherited, several years ago scientists identified the gene defects responsible for a less common, inherited form of ALS. Using genetic engineering, researchers developed strains of mice that express this gene defect and mimic the human disease. Researchers have now shown that injections of minocycline slow the onset and delay progression of symptoms in ALS mice. Minocycline is approved by the FDA as an antibiotic, but the drug appears to be working here in a different way, by interfering with the "cell suicide" process. Because minocycline works differently from riluzole, the only drug now approved for ALS, a combination may be more effective than either drug alone. Researchers are investigating that possibility.

*Transplantation of mouse embryonic stem cells in animal models of Parkinson's disease:* The loss of nerve cells that make the neurotransmitter dopamine is a central feature of Parkinson's disease. A team of scientists directly transplanted mouse embryonic stem cells into the brains of rats with cell loss similar to Parkinson's. Some of these cells formed dopamine nerve cells that integrated into the rats' brains sufficiently well to restore normal behavior on motor tasks. Another group of researchers first added a gene (called Nurr1) to embryonic mouse stem cells in cell culture and then exposed the cells to a series of growth factors that caused them to develop into dopamine producing nerve cells. When transplanted into rat brains, these nerve cells also made dopamine, showed the electrical properties expected of normal dopamine neurons, and formed functional connections that reduced Parkinson's-like symptoms. It is important to note that, in the first study, some transplanted cells grew into uncontrolled tumors, illustrating the need for more research before embryonic stem cell transplantation is safe for human patients.

*Genetic and environmental factors in hemorrhagic stroke:* A hemorrhagic stroke occurs when a blood vessel ruptures, bleeding into the brain. These strokes are often fatal (perhaps 40 to 50 percent of cases), or cause serious disability and require expensive care. Because bleeding stroke is less common than stroke from a blocked blood vessel, the risk factors are not as well understood. The Genetic and Environmental Risk Factors for Hemorrhagic Stroke Study is designed to identify environmental risk factors for hemorrhagic stroke. Early data from this ongoing study confirms the significant influence of genetic factors. Yet, the results indicate that even among people who inherit an increased risk, modifiable factors, such as smoking, hypertension, and alcohol use, also play an important role. Once completed, the detailed results of the study should help identify people at higher risk for this devastating type of stroke and provide guidance for reducing risk.

*Coenzyme Q10 may slow the progression of Parkinson's Disease:* Results of the first placebo-controlled, clinical trial of the compound coenzyme Q10 suggest that it may slow disease progression in patients with early-stage Parkinson's disease (PD). Coenzyme Q10 is a natural chemical that is important in the function of mitochondria, the cells' energy factories, and may help combat damaging free radicals. While the results of this small trial are preliminary and must be confirmed in a larger study, they provide hope that this compound may ultimately provide a new way of treating PD.

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## Story of Discovery: Lysosomal Storage Diseases

The lysosomal storage diseases (LSDs) defied the best efforts of medical science since physicians first recognized these inherited disorders in the 19th century. However, persistent research focused on the LSDs, coupled with advances arising from fundamental biology, are bringing progress in understanding, diagnosing, preventing, and treating these diseases.

We now group more than 40 disorders as LSDs. Each occurs when storage material accumulates in a recycling compartment of cells called the lysosome. The material accumulates because an inherited defective enzyme–a different enzyme in each disease–fails to break down certain complex biological molecules. The accumulating materials damage cells, leading to a host of problems that can involve the brain, heart, kidneys, spleen, the skeletal system, and the eye. In the most serious cases, an infant at first develops normally, then progressively loses even the most basic abilities and dies. In other cases, symptoms may be quite mild, first appearing in adulthood. Even a single disorder can produce a wide range of symptoms and severity in different people, further complicating the picture for these diseases.

In the 1920's and 30's researchers, relying upon advances in fundamental biochemical science, began to make inroads into understanding the LSDs by identifying the complex lipids (fatty chemicals) that were accumulating in the brain and other organs. Lipids provide electrically insulating covering for nerve fibers, are a crucial component of cell membranes, and serve many other normal functions. Why these lipids were building up in LSDs was a mystery. Since the 1950's, Dr. Roscoe Brady, in the NINDS intramural research program, has led a pioneering research team that has improved the understanding, diagnosis, and treatment of LSDs. Building on knowledge from studies of the normal metabolism of lipids, the researchers determined that patients with Gaucher disease, an LSD, accumulate the lipid glucocerebroside because they inherit a defect in the enzyme glucocerebrosidase. The critical studies used newly emerging technology for tagging chemicals in the body with trace radioactive substances to follow metabolism.

Having identified defective glucocerebrosidase as the culprit in Gaucher disease, replacing the missing enzyme seemed a logical approach to therapy. However, it took eight years to develop methods to purify enough glucocerebrosidase from human placental tissue to attempt treatment in just two patients. The results were encouraging. The NINDS research team, working with a private biotechnology company, went on to develop a method that not only produced sufficient quantities of glucocerbrosidase, but also modified the enzyme so that cells were more likely to take it up where it was needed. Clinical trials demonstrated that enzyme replacement therapy dramatically improves quality of life for people with Gaucher disease.

Following the pattern for attacking Gaucher disease, Dr. Brady's team subsequently identified the specific enzyme defects in Niemann-Pick, Tay-Sachs, and Fabry diseases. They and other scientists have now determined the defects in more than 40 LSDs. For some of these disorders enzyme therapy is also proving effective. For example, last year an NINDS clinical trial demonstrated that enzyme therapy for Fabry disease provides widespread benefit for patients with the disorder. The enzyme reduced the level of severe pain, improved pain-related quality of life, and appeared to reduce kidney problems and improve cardiac function. Trials for enzyme replacement therapy in other LSDs, such as the mucopolysaccharidoses, are underway here and abroad.

Enzyme therapy for Gaucher and Fabry diseases is a remarkable achievement. It has saved or dramatically improved thousands of lives and demonstrated the feasibility of this approach for several other diseases. However, it is not the final answer for the LSDs. Enzyme therapy is extremely expensive and, more importantly, it cannot address the brain dysfunction caused by LSDs. The blood-brain barrier, which protects sensitive brain cells from potentially toxic chemicals in the general circulation, also prevents large molecules such as enzymes from reaching brain cells. Researchers are developing other strategies for treatment. One approach currently under testing capitalizes on detailed understanding of the biochemical pathways by which cells make lipids. Scientists have developed drugs to reduce the synthesis of lipids that lead to storage products in the brain in LSDs, and thereby minimize the accumulation of harmful substances. Following promising findings in animal models of LSDs, this therapeutic strategy is now being tested in patients.

The advent of the molecular biology era has opened another approach for attacking these diseases. Various research teams here and around the world have identified the specific gene defects responsible for most of the LSDs. This has enabled scientists to develop tests that improve diagnosis and carrier screening. Most LSDs are recessively inherited. A child must inherit a defective gene from both parents to acquire the disease, and carriers of one gene usually show no overt signs of the disorder. Since some of these diseases are concentrated in specific population groups, carrier screening can be crucial. For some diseases, such as Tay-Sachs, screening, with genetic counseling, has dramatically reduced the number of new cases.

The advances in molecular genetics have also offered the tantalizing hope of gene therapy to replace or repair the defects that cause LSDs. Gene therapy is a deceptively simple idea which is extraordinarily difficult to carry out safely and effectively. For the LSDs this is particularly so because the gene must be supplied to cells throughout the body, including the brain. The brain is an especially difficult target for gene therapy, not only because of the blood-brain barrier, but also because nerve cells do not divide and thus are not amenable to the most common strategies to introduce genes. Nonetheless, there has been encouraging progress toward developing gene therapy for LSDs. Relying upon natural mutations and genetic engineering, scientists have developed strains of mice that mimic several human LSDs. These mice provide models for testing potential approaches to gene therapy. Dr. Brady's group provided the first successful safety test for this approach in people in 1995, and efforts by several research teams are now underway.

Gaucher disease was first reported in the medical literature in 1882. By the 1920's biochemical science had advanced sufficiently to identify the chemical that accumulates in this disorder, but it wasn't until the 1950's, with advances in radioactive tracer chemistry, that scientists could begin to determine just why this was occurring. It took five years to discover the enzyme defect, eight more years to purify enough enzyme for the first human tests, and sixteen years more to get enough enzyme to treat many patients and establish the effectiveness of enzyme replacement therapy. Gene therapy, and other new approaches, hold tremendous promise for the future, but will require similar ingenuity and long-term commitment to develop into safe and effective treatments.

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## INITIATIVES

NINDS continues its emphasis on investigator-initiated research proposals from scientists and physicians throughout the nation, as is appropriate to the challenges posed by neurological diseases. The Institute engages in directed programs when public health needs dictate, unusual scientific opportunities arise, or bottlenecks to progress warrant a more active approach. The following highlights enhancements to ongoing programs and new initiatives:

Cross-cutting programs:

*Clinical trials:* NINDS has designed and conducted pioneering clinical trials to test the safety and effectiveness of interventions to prevent and treat neurological disorders. In recent years, the Institute has augmented clinical trials activities to capitalize on the opportunities emerging from

progress in neuroscience. NINDS has implemented new grant mechanisms for planning trials and for pilot trials, developed procedures to optimize trial design, increased professional staff to support trial design and monitoring, and created a subcommittee of the NANDS Council to provide broad programmatic and priority-setting advice on Institute clinical research activities, including clinical trials. In the coming year, the Institute is exploring options for creating a network of potential physician-investigators for neurological clinical trials, and is initiating a program of supplements to capture potentially useful genetic samples in ongoing clinical trials.

Ongoing clinical trials, in both intramural and extramural divisions, focus on prevention and on treatment. Studies range from planning, through small phase I and II investigations, to large phase III multi-center projects. Trial interventions include drugs, surgery, gene transfer, chronic brain stimulation, hormone therapy, cell transplantation, hypothermia, radiosurgery, immunotherapy, vaccines, vitamins, behavioral management, physical therapy, and psycho-social methods. A partial list of disorders targeted in ongoing trials includes: AIDS, ALS, attention deficit hyperactivity disorder, autism, traumatic brain injury, brain tumors, cerebral palsy, chronic pain, dystonia, headache, epilepsy, Fabry disease, Gaucher disease, Herpes zoster, HIV, Lyme disease, migraine, multiple sclerosis, Parkinson's disease, sleep disorders, surgical pain, and stroke.

Two major trials in Parkinson's disease highlight activities of the clinical trials program. NINDS has embarked upon a large trial of neuroprotective drugs for Parkinson's disease, that is, drugs that slow or stop disease progression rather than masking symptoms. The Institute is working with academia and industry to select the best drugs for testing and is setting up a network of more than 40 clinical centers and a statistical and data coordinating center to carry out the trial. NINDS is working with voluntary groups to recruit patients and may begin the first pilot studies as early as spring 2003. The Institute is also undertaking, in cooperation with the U.S. Department of Veterans Affairs, the largest ever trial to compare the effectiveness of deep brain stimulation (DBS) with best medical management. The DBS trial will further evaluate which of two brain regions is better for this purpose. Deep brain stimulation uses implanted electrical devices to compensate for unbalanced movement control circuits in the brain.

*Translational research:* Translational research bridges between the fundamental discoveries about the brain and disease and early stage clinical trials. NINDS has a long history of translational research. Since 1975, the NINDS Anticonvulsant Screening Project (ASP) (formerly part of the Antiepileptic Drug Development (ADD) Program) has worked with industry to test more than 20,000 compounds for their anti-convulsant properties, including drugs now in use. Similarly, the NINDS Neural Prosthesis program has for three decades fostered the development of devices now used to help people with hearing impairments and spinal cord injuries. The unique advantages of the NINDS intramural research program have been especially suited to fostering success in the translational arena as well. Enzyme therapy for Gaucher and Fabry disease, innovative approaches to brain tumor treatment, and vaccine approaches to stroke prevention are among the many examples.

Recent NINDS strategic planning panels and numerous scientific workshops have noted the importance of translational research as scientific progress presents increasing opportunities for fighting neurological disorders. In July 2002, the Institute issued solicitations to initiate a

comprehensive program designed to support translational research efforts. Essential to this program are peer review criteria tailored to the needs of translational research as well as milestone driven funding, which is common in industry. The program emphasizes cooperation among researchers and between NINDS staff and the research team. The goal is to provide an environment where coalitions of basic scientists, clinicians, and company representatives can design and carry out drug discovery and other preclinical studies required to bring therapeutic candidates to the point where clinical trials begin. A consortium to develop gene therapy for Parkinson's disease is the first project funded in this program.

Complementing the new translational program are several specific NINDS efforts within the realm of translational research, including:

- In FY02 the Institute formed and funded a consortium of investigators to test more than 1000 drugs against 29 rapid laboratory assays (tests) for possible activity against neurological disease. The group is analyzing data from the various assays collectively to capitalize on the common mechanisms contributing to various diseases. The best candidate chemicals are moving on to further testing in animal models through a supplement program. Most of the drugs in this collection have been previously approved by the FDA for other purposes, so positive results might move quickly to human trials.
- The Institute has awarded a contract for a high throughput drug screening center. High throughput screening (HTS) rapidly tests large numbers of chemicals to find lead compounds for drug development. Although the technology is widely used in industry, most neurological diseases are not sufficiently common to support commercial screening programs. NINDS is also soliciting proposals for the development of screening tests which can be adapted for high throughput screening.
- NINDS is revitalizing its long-term engagement in developing better drugs for epilepsy. Guided by the epilepsy benchmarks planning process, increasing efforts will focus on drugs to prevent the development of epilepsy and for treatment resistant epilepsy, as well as continuing efforts to develop better drugs with minimal side effects.
- Spinal muscular atrophy (SMA) is the focus of a targeted intramural-extramural translational research program which will attempt to develop therapies for this disease. This program will also serve as a pilot for testing innovative contract based approaches for expediting translational research. In the last few years, the discovery of the gene defects responsible for SMA and the development of animal models that mimic the human disease have made SMA an excellent candidate for such an approach.
- The neural prosthesis program is continuing to develop electronic and mechanical devices that connect to the nervous system and help compensate for abilities lost through disease or injury. Understanding the mechanisms and improving the technology for deep brain stimulation is a major focus with potential application to many neurological disorders.
- The Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS) will help develop rapid diagnosis and interventions for stroke, bringing together researchers within each SPOTRIAS and across programs.

*Encouraging cooperation:* Increasingly, progress against neurological disorders requires cooperation among multi-disciplinary teams of investigators. NINDS strategic planning panels and disease specific planning efforts have emphasized the importance of facilitating cooperation

among scientists. The Institute continues to support meritorious investigator-initiated program project and center grants that bring together teams of researchers. NINDS is also enhancing support for sharing of data and resources and for collaborative efforts through a variety of other mechanisms, as the following examples illustrate:

- Center Core Grants will support shared resources for NINDS funded investigators, including facilities for animal models, cell culture, computer modeling, DNA sequencing, drug screening, gene vectors, imaging, mass spectrometry, microarrays, microscopy, molecular biology, proteomics or other common needs that arise.
- The NINDS Cooperative Program in Translational Research, as its name suggests, uses cooperative agreements to facilitate partnerships between basic and clinical investigators, and to stimulate agreements between the academic and industrial sectors.
- NINDS, working with other components of NIH, is soliciting proposals for research centers of excellence in autism and in muscular dystrophy, as well as for planning grants to develop proposals for additional centers.
- The NINDS Morris K. Udall Parkinson's Disease Research Centers of Excellence not only bring investigators together at each center, but also work together as a consortium toward their common goal. NINDS is soliciting proposals to continue this program.
- The Deep Brain Stimulation Consortium is modeled along the lines of the consortium developed by the NINDS Neural Prosthesis Program, which is continuing into its fourth decade.
- Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS) will support collaborations of clinical researchers from different specialties, working toward the common goals of promoting rapid diagnosis and the use of effective interventions that reduce the disability and mortality from stroke.
- Multimodal Integration Research Networks in Cognitive Neuroscience will form cross-disciplinary networks of scientists interested in studying the neural mechanisms of cognition and other complex behaviors.
- NINDS is working with the National Cancer Institute to support Specialized Programs of Research Excellence (SPOREs) focused on brain tumors.
- Targeted administrative supplements will encourage collaboration and cooperation among laboratories where research on traumatic brain injury, stroke, or neurodegenerative disorders could be combined.
- In the NINDS intramural program, the NIH John Edward Porter National Neuroscience Center center will bring together scientists from ten NIH components involved in brain related research (NIMH, NINDS, NICHD, NIDCD, NHGRI, NEI, NIDA, NIAAA, NIDCR, NIA) and will be managed as an inter-Institute resource.
- Specific Institute programs also facilitate sharing of resources and data in broad areas such as complex genetics, transgenic mouse models, drug screening, and bioengineering, as well as more disease-focused areas such as the transmissible spongiform encephalopathies and health disparities research.

*Workshops:* NINDS supports scientific workshops focused on specific diseases, cross-cutting research themes, emerging technologies, and specific clinical issues. Workshops assess the state of science, foster collaborations, attract scientists from other disciplines, and help the Institute determine how best to stimulate progress. Most workshops are held in cooperation with other

components of NIH and with voluntary health organizations, as appropriate. Recent workshops focused on reflex sympathetic dystrophy/complex regional pain syndrome, epilepsy genetics, resources for transmissible spongiform encephalopathies (TSE) research, Joubert syndrome, neurobiology of craniofacial/deep tissue persistent pain, brain banking, tuberous sclerosis complex, astrocyte function, mucopolysaccharidoses, familial dysautonomia, DNA microarrays for epilepsy research, exploring the options for clinical trials networks, metabolic disorders, compound libraries for drug discovery in neurological disorders, progressive multifocal leukoencephalopathy, models of epileptogenesis and treatment-resistant epilepsy, the role of neuroimaging in clinical trials for Parkinson's disease, proteomics in the neurosciences, and health disparities in stroke and in epilepsy, as well as including annual meetings of groups such as the Neural Prosthesis and the Deep Brain Stimulation Consortia and the Morris K. Udall Parkinson's Disease Centers of Excellence. Among the workshops planned for the future are meetings focused on imaging in epilepsy, career development for minority/disability investigators, clinical research in the treatment of intracerebral hemorrhage, the molecular mechanisms of synaptic plasticity, novel approaches to gene therapy for neurobehavioral disorders, biomarkers in multiple sclerosis, and translating promising strategies for spinal cord injury therapy.

*Stem cells:* Because of the limited capacity of the brain and spinal cord to repair themselves, stem cells hold enormous promise for neurological diseases. Reinforcing this view is the rapidly accumulating evidence for stem cell therapies in animal models of disorders such as Parkinson's disease, spinal cord injury, ALS, inherited metabolic diseases, multiple sclerosis, brain tumors, stroke and many other disorders. Stem cells might lead to useful therapies by replacing lost cells, providing a substrate for regrowth, carrying needed genes or enzymes, delivering growth factors, targeting drugs to brain tumors, or in numerous other ways. Even the adult brain harbors neural stem cells, so encouraging these cells in the brain and spinal cord to help repair damage is yet another option to explore. The enthusiasm for the potential of neural stem cells must be tempered by a recognition that stem cells might also do harm, reinforcing the need for understanding of the basic biology of these cells.

For many years, NINDS has supported ground breaking work on animal stem cells and on adult human stem cells. The Institute is enhancing its stem cell activities with support for scientific workshops and for solicitations to encourage research and training in the use of all forms of stem cells in animals and adult humans, and on human embryonic stem cells, in accordance with the President's guidelines. Among ongoing efforts are solicitations on the biology of non-human stem cells in the environment of the nervous system, on the plasticity of human stem cells in the nervous system, on novel approaches to enhance animal stem cell research, and for short-term courses in human embryonic stem cell culture. To expedite research on human embryonic stem cells, NINDS is supplementing current grantees with expertise in stem cell research to extend their work to compare human embryonic stem cells with other types of stem cells. NINDS Intramural investigators, who are world leaders in stem cell research, were among the first to gain access to Federally-approved human embryonic stem cells. The Institute is also working with the FDA to develop an interagency collaboration to enhance and expedite the translation of promising animal research on therapies such as cell transplantation and gene therapy to well-designed clinical studies for treating neurological disorders.

*Genetics:* Because so many of our genes are important in brain function, it is not surprising that there are hundreds of disorders caused by defects in single genes. Scientists have identified the gene mutations responsible for more than 200 neurological disorders. In the last year, for example, research identified gene defects responsible for types of muscular dystrophy, amyotrophic lateral sclerosis (ALS), epilepsy, and hereditary spastic paraplegia, and identified chromosomal regions that contain genes related to migraine and to restless legs syndrome. Progress in genetics has implications far beyond inherited disorders of the brain. Animal models based on gene findings are helping research on the common non-familial forms of Alzheimer's, ALS, and Parkinson's, and researchers are beginning to confront the complex interactions between multiple genes and the environment that determine susceptibility to most disorders. Molecular genetics is also a scalpel to dissect processes in the normal brain.

Because of the cross-cutting impact of neurogenetics, research in this area continues to be a major priority for NINDS. The Institute supports many scientific workshops focused on particular genetic disorders, often in cooperation with private groups and with other components of NIH such as the Office of Rare Diseases. NINDS recently expanded its research program on gene discovery and in gene therapy with solicitations targeted to those areas. The Institute is undertaking a new initiative focusing on complex genetic contributions to neurological and neurobehavioral disorders, that is, the multiple genes that contribute to susceptibility and progression of most common disorders. To support such efforts, the Institute has created the NINDS Human Genetics Repository, which will initially focus on gathering materials and clinical data to support investigations of stroke, epilepsy, and Parkinson's disease, and expand in the future to other diseases. The Institute will supplement ongoing NINDS clinical trials to facilitate building this resource. NINDS is also supplementing investigators to ensure that genetically engineered mouse models are widely available.

Disease-specific programs:
Given the large number of neurological disorders, the following highlights can not encompass all NINDS disease-specific activities, but illustrate the range of efforts underway.

*Stroke:* The NINDS stroke research program ranges from basic investigation of stroke mechanisms through large studies of risk factors and clinical trials aimed at prevention or treatment. Interventions under investigation include drugs, surgery, vitamins, physical therapy, and psychosocial modalities. Research is also targeted to special issues of stroke in geographic regions ("the stroke belt"), minority populations, women, and children.

NINDS is continuing a strategic planning process for stroke research in the form of a Stroke Progress Review Group (PRG). As part of that process, in July 2001, the NINDS held a meeting of 150 nationally and internationally recognized stroke experts that included clinicians, representatives from voluntary health organizations and the advocacy community. The group has issued a report that identifies critical gaps in stroke knowledge and sets research priorities, and an NIH working group is mapping ongoing research to these needs and developing implementation plans. The PRG met in January 2003 to discuss further efforts to implement the report. In November 2002, NINDS also convened a planning panel focusing on health disparities in stroke.

Several major stroke research initiatives are planned or underway. The Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS) will help develop rapid diagnosis and interventions. With regard to genetics, stroke is among the disorders included in the new NINDS Human Genetic Repository, and the Institute will provide administrative supplements to ongoing clinical trials to encourage participation. The Stroke Prevention/Intervention Research Program (SPIRP) will address issues related to minority populations and the "stroke belt." NINDS held a November 2002 workshop focused on stroke health disparities, and is planning meetings on intracerebral hemorrhage, and on primary prevention to help guide further efforts in those areas. The blood-brain barrier was highlighted as a priority of the Stroke PRG, the Brain Tumor PRG, and other NINDS strategic and disease specific planning groups; an NINDS solicitation will address needs in this critical area of research. The NINDS intramural stroke program is also continuing its efforts. For example, intramural scientists are pursuing a vaccine strategy for prevention, and a 24-hour acute stroke research program in diagnosis and treatment at Suburban Hospital in Bethesda, Maryland, is continuing, with plans to replicate this program in another medical facility that serves predominantly inner city minority populations. The Institute is also enhancing its efforts, in cooperation with private groups, to improve public awareness of stroke and the need for rapid treatment.

*Muscular dystrophy:* In May 2000, NINDS, working with NIAMS and with voluntary health organizations, held scientific workshops focused on Duchenne muscular dystrophy and on facioscapulohumeral muscular dystrophy (FSHD). Subsequent solicitations were successful in substantially expanding NIH research on the muscular dystrophies. Efforts to stimulate muscular dystrophy research, in accordance with the 2001 MD-CARE Act, are continuing. NIH has requested and received delegation of authority from the Secretary to form the interagency Muscular Dystrophy Coordinating Committee (MDCC). NIH has also created a Muscular Dystrophy Research Task Force, including scientists from NIH and the extramural community as well as representative of private muscular dystrophy groups, which complements the MDCC. With guidance from discussions of this group, NIH is soliciting proposals for Muscular Dystrophy Cooperative Centers and for grants to develop potential future centers. Programs to help train researchers in this field are also planned.

*Epilepsy:* The NINDS epilepsy research program is building on the momentum established by the landmark March 2000 conference "Curing Epilepsy: Focus on the Future." The conference marked a shift of goals toward curing epilepsy, defined as "no seizures/no side-effects of treatment," or preventing epilepsy from beginning. Since the meeting, epilepsy researchers, private health advocates, and NINDS staff have formulated a series of "benchmarks" for epilepsy research. For each benchmark, a "steward," who is an expert from the epilepsy clinical or scientific community, monitors progress and informs NINDS and the group on needs and opportunities for research to accomplish the benchmark. The epilepsy stewards met most recently in December 2002 to discuss progress and future efforts to address the benchmarks. Training new investigators is important for accomplishing many of the benchmarks, and NINDS began efforts to encourage participation of young investigators at the conference itself and has undertaken subsequent efforts to foster collaborations of new investigators with established researchers. Another critical need, which has been the subject of two NINDS workshops, is for development and validation of animal models, especially to support the goals of preventing epilepsy from becoming established (epileptogenesis) and finding better ways to address

treatment resistant epilepsy. The NINDS Anticonvulsant Screening Project (formerly part of the Antiepileptic Drug Development program), which has played a significant role in developing medications over the last three decades, is being renewed and revitalized, with increased attention to drugs targeting epileptogenesis and treatment resistant epilepsy.

*Parkinson's disease:* In March 2000, as requested by Congress, NIH submitted the NIH Parkinson's Disease Research Agenda. This research plan was developed through extensive interactions with the scientific and health advocacy communities. In January 2002, NIH held a meeting of the Parkinson's Consortium to update that effort, and in July 2002, the NIH Director held a scientific "summit" with Parkinson's scientists to identify roadblocks to progress. These and ongoing meetings of the NIH Parkinson's Disease Coordinating Committee are guiding efforts focused on Parkinson's disease.

NIH and NINDS are aggressively implementing the Agenda, with over twenty grant solicitations, workshops and other activities in the past three years, and more underway. These efforts target every critical research area in the Agenda, including genetics, environmental factors, cell death, pharmacological treatments, deep brain stimulation, gene therapy, stem cell research, dyskinesias, imaging, animal models, and the non-motor effects of Parkinson's, including cognitive and emotional problems associated with the disease. The number of NINDS-initiated Parkinson's disease research activities undertaken since the inception of the Agenda has far exceeded that for any other disease in the history of the Institute. NIH/NINDS will continue to implement the Agenda, focusing on the recommendations made at the January 2002 Consortium and the July 2002 summit meeting to guide further efforts.

*AIDS:* HIV infection causes significant neurological problems in a large percentage of persons with AIDS. Most of the HAART (high activity antiretroviral therapy) drugs do not cross the blood-brain barrier. Thus, there is concern that the brain may serve as a reservoir for HIV. The NINDS AIDS research program supports studies that investigate HIV entry and persistence in the nervous system, the mechanisms of viral factors injurious to the nervous system, and development of new treatments for the HIV CNS infection and related opportunistic infections and malignancies. The Institute continues its support for the Neurologic AIDS Research Consortium, which carries out clinical trials, and for the National NeuroAIDS Tissue Consortium. NINDS is developing a new program that will enable domestic and international investigators experienced in HIV research to collaborate with institutions in developing countries where there is a critical need for basic and clinical research support. In order to ensure that a new generation of scientists are appropriately trained to continue advancements in neuroAIDS, the Institute will issue a series of solicitations focused on training at levels from pre-doctoral through junior faculty. NINDS is joining with NIMH in a multicenter study of the impact of HAART on dementias in AIDS patients. The NINDS Intramural Program, which has made significant advances in understanding the neurological complications of HIV infection, is expanding its clinical and basic research efforts related to AIDS. The Institute also continues to hold scientific workshops in this area, most recently a November 2002 meeting on "Viral and host genetics factors regulating HIV/CNS."

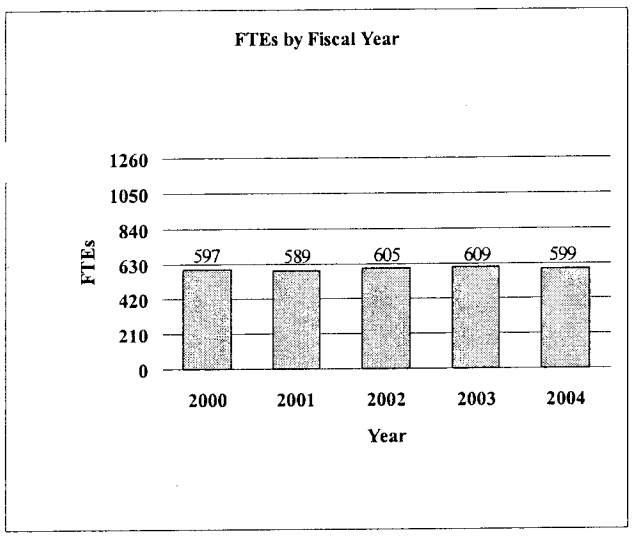
*Health disparities:* In May 2000, NINDS issued a Five Year Strategic Plan on Minority Health Disparities. The NINDS Office of Minority and Health Research is leading implementation of

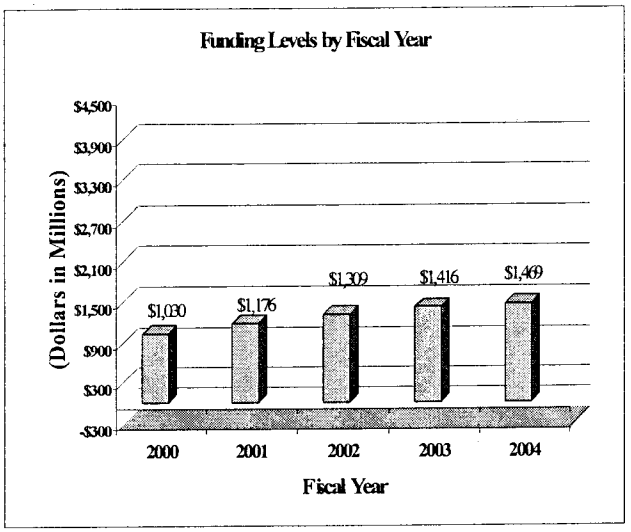
this plan, with workshops, solicitations, and an extensive program of research and training related to health disparities. Planning meetings focused on epilepsy and stroke held in the Fall 2002, and an earlier meeting on neuroAIDS, are guiding efforts. The Specialized Neuroscience Research Programs (SNRPs) are designed to augment and strengthen the research capabilities of faculty, students, and fellows at minority institutions by supporting the development or enhancement of basic and clinical neuroscience research projects and programs. The SNRP program continues to be an integral part of NINDS efforts and has been expanded to include 10 SNRPS. New initiatives include an Alaska native stroke registry, the Stroke Prevention/Intervention Research Program (SPIRP), a collaboration with NHLBI on the Jackson Heart Study (stroke), and the Neuroscience Scholars Program.

*Other:* NINDS is enhancing programs or undertaking new initiatives in several other areas of basic and clinical neuroscience. These include reflex sympathetic dystrophy, craniofacial/deep tissue persistent pain, transmissible spongiform encephalopathies, training and career development, computational neuroscience, neuroimaging informatics, research integrity, cognitive neuroscience, and the activation of natural nerve cell growth and survival mechanisms by the environment. The Institute continues to cooperate on initiatives led by other components of NIH that are relevant to the NINDS mission in areas such as bioengineering, genetics, international programs, loan repayment, imaging, diabetes, rehabilitation, behavioral disorders, autoimmune diseases, and the neurologic effects of cardiopulmonary resuscitation.

## BUDGET POLICY

The Fiscal Year 2004 budget request for the NINDS is $1,468,926,000, including AIDS, an increase of $52,505,000 and 3.7 percent over the FY 2003 amended President's Budget Request. A five year history of FTEs and Funding Levels for NINDS are shown in the graphs below. Note that Fiscal Years 2001 and 2000 FTEs are not comparable for the NIH Human Resources functional consolidation.



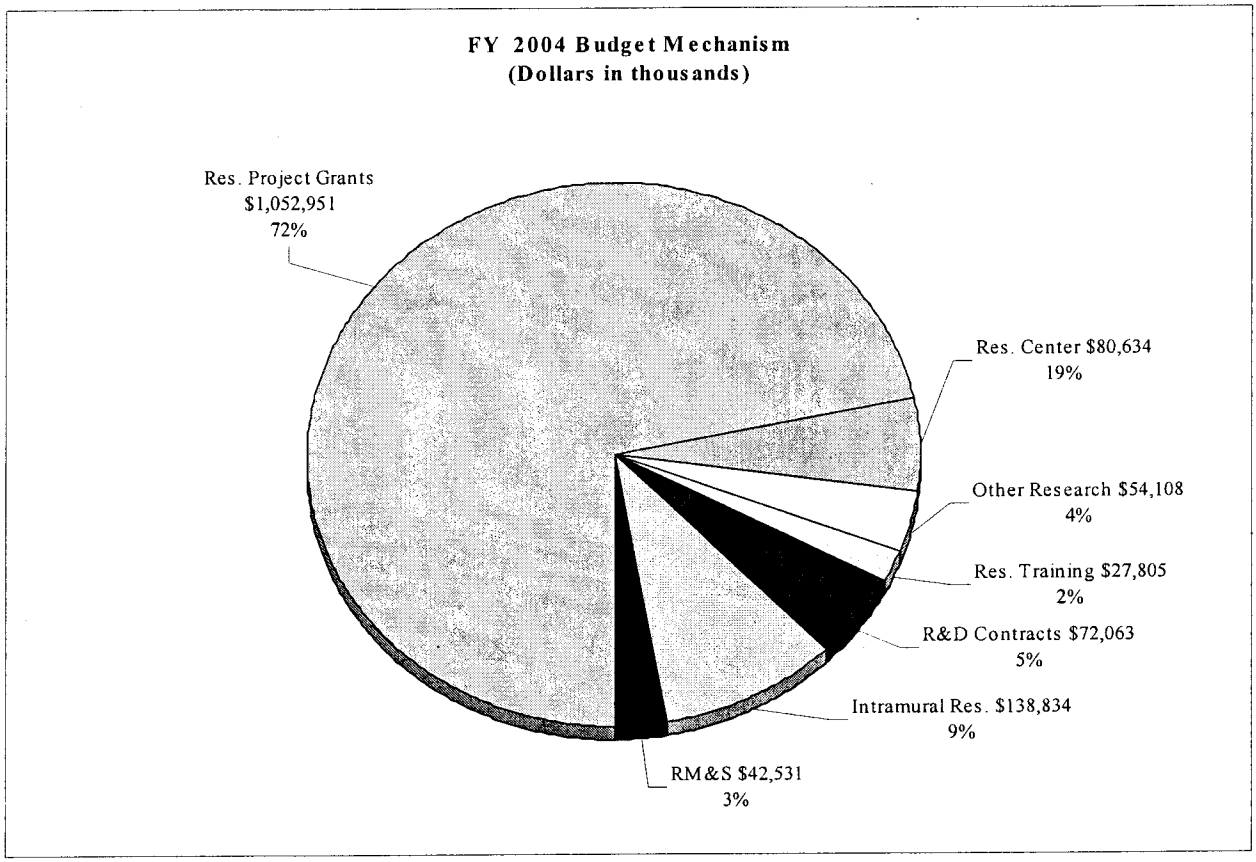

NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. NINDS will provide an aggregate average cost increase of 3.2 percent for RPGs.

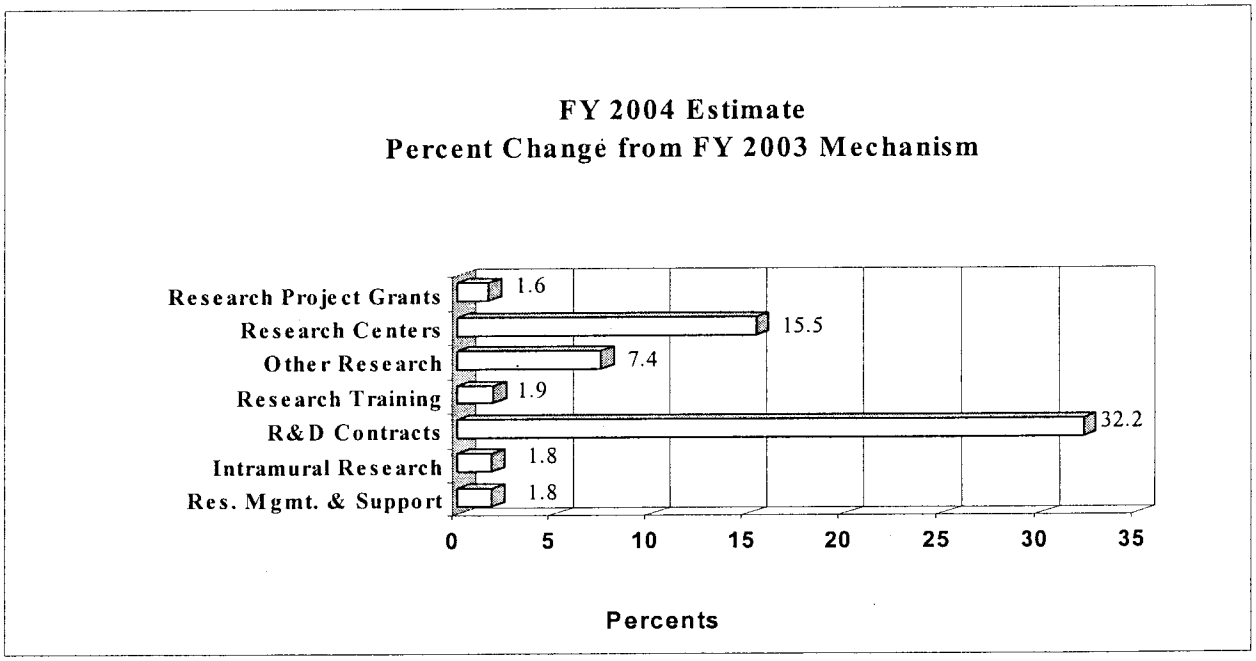
Also in FY 2004, NINDS will fully fund 18 grants including 11 Academic Research Enhancement Awards , and 7 Small Research Grants.

Promises for advancement in medical research are dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2004 request, NINDS will support 704 pre- and postdoctoral trainees in full-time training positions, the same number as in FY 2003. Stipend levels for NRSA trainees will increase by 4 percent over Fiscal Year 2003 levels for predoctoral fellows, and from 4-1 percent, based on years of experience, for postdoctoral fellows.

The Fiscal Year 2004 request includes funding for 63 research centers, 323 other research grants, including 223 clinical career awards and 71 R&D contracts including $768 thousand for Best Pharmaceuticals for Children's Act. Intramural Research and Research Management and Support receive increases of 1.8 percent over FY 2003.

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 2002 Actual | | FY 2003 Amended President's Budget | | FY 2004 Estimate | |
|---|---|---|---|---|---|---|
| Research Grants: | No. | Amount | No. | Amount | No. | Amount |
| Research Projects: | | | | | | |
| Noncompeting | 1,951 | $687,109,000 | 2,001 | $755,218,000 | 1,885 | $740,545,000 |
| Administrative supplements | (160) | 7,233,000 | (200) | 12,000,000 | (200) | 12,000,000 |
| Full funded | 0 | 0 | 0 | 0 | 18 | 2,595,000 |
| Single year | 666 | 237,698,000 | 641 | 237,649,000 | 704 | 263,638,000 |
| Subtotal, competing | 666 | 237,698,000 | 641 | 237,649,000 | 722 | 266,233,000 |
| Subtotal, RPGs | 2,617 | 932,040,000 | 2,642 | 1,004,867,000 | 2,607 | 1,018,778,000 |
| SBIR/STTR | 107 | 28,900,000 | 97 | 31,388,000 | 105 | 34,173,000 |
| Subtotal, RPGs | 2,724 | 960,940,000 | 2,739 | 1,036,255,000 | 2,712 | 1,052,951,000 |
| Research Centers: | | | | | | |
| Specialized/comprehensive | 49 | 59,251,000 | 58 | 69,840,000 | 63 | 80,634,000 |
| 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 | 49 | 59,251,000 | 58 | 69,840,000 | 63 | 80,634,000 |
| Other Research: | | | | | | |
| Research careers | 191 | 27,599,000 | 211 | 30,579,000 | 223 | 32,318,000 |
| Cancer education | 0 | 0 | 0 | 0 | 0 | 0 |
| Cooperative clinical research | 42 | 7,095,000 | 45 | 7,300,000 | 47 | 7,800,000 |
| Biomedical research support | 0 | 0 | 0 | 0 | 0 | 0 |
| Minority biomedical research support | 6 | 1,720,000 | 9 | 2,565,000 | 10 | 3,065,000 |
| Other | 40 | 11,960,000 | 38 | 9,925,000 | 43 | 10,925,000 |
| Subtotal, Other Research | 279 | 48,374,000 | 303 | 50,369,000 | 323 | 54,108,000 |
| Total Research Grants | 3,052 | 1,068,565,000 | 3,100 | 1,156,464,000 | 3,098 | 1,187,693,000 |
| Research Training: | FTTPs | | FTTPs | | FTTPs | |
| Individual awards | 296 | 11,097,000 | 296 | 11,452,000 | 296 | 11,681,000 |
| Institutional awards | 408 | 15,416,000 | 408 | 15,847,000 | 408 | 16,124,000 |
| Total, Training | 704 | 26,513,000 | 704 | 27,299,000 | 704 | 27,805,000 |
| Research & development contracts | 42 | 50,895,000 | 63 | 54,500,000 | 71 | 72,063,000 |
| (SBIR/STTR) | (10) | (2,800,000) | (10) | (1,100,000) | (10) | (1,100,000) |
| | FTEs | | FTEs | | FTEs | |
| Intramural research | 424 | 125,119,000 | 419 | 136,379,000 | 412 | 138,834,000 |
| Research management and support | 181 | 38,326,000 | 190 | 41,779,000 | 187 | 42,531,000 |
| Cancer prevention & control | 0 | 0 | 0 | 0 | 0 | 0 |
| Construction | | 0 | | 0 | | 0 |
| Total, NINDS | 605 | 1,309,418,000 | 609 | 1,416,421,000 | 599 | 1,468,926,000 |
| (Clinical Trials) | | (98,934,000) | | (113,493,000) | | (115,760,000) |

**NATIONAL INSTITUTES OF HEALTH**
**National Institute of Neurological Disorders and Stroke**

**Budget Authority by Activity**
**(dollars in thousands)**

| ACTIVITY | FY 2002 Actual | | FY 2003 Amended President's Budget | | FY 2004 Estimate | | Change | |
|---|---|---|---|---|---|---|---|---|
| | FTEs | Amount | FTEs | Amount | FTEs | Amount | FTEs | Amount |
| Extramural Research: | | $1,145,973 | | $1,238,263 | | $1,287,561 | | $49,298 |
| Subtotal, Extramural research | | 1,145,973 | | 1,238,263 | | 1,287,561 | 0 | 49,298 |
| Intramural research | 424 | 125,119 | 419 | 136,379 | 412 | 138,834 | (7) | 2,455 |
| Res. management & support | 181 | 38,326 | 190 | 41,779 | 187 | 42,531 | (3) | 752 |
| Cancer Control & Prevention | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 605 | 1,309,418 | 609 | 1,416,421 | 599 | 1,468,926 | (10) | 52,505 |

## NATIONAL INSTITUTES OF HEALTH
### National Institute of Neurological Disorders and Stroke

**Summary of Changes**

| | | | | |
|---|---|---|---|---|
| 2003 Amended President's Budget | | | | $1,416,421,000 |
| 2004 Estimated Budget Authority | | | | 1,468,926,000 |
| Net change | | | | 52,505,000 |
| | 2003 Amended President's Budget Base | | Change from Base | |
| CHANGES | FTEs | Budget Authority | FTEs | Budget Authority |
| A. Built-in: | | | | |
| 1. Intramural research: | | | | |
| a. Within grade increase | | $35,795,000 | | $614,000 |
| b. Annualization of January 2003 pay increase | | 35,795,000 | | 277,000 |
| c. January 2004 pay increase | | 35,795,000 | | 537,000 |
| d. One extra day of pay | | 35,795,000 | | 138,000 |
| e. Payment for centrally furnished services | | 22,446,000 | | 449,000 |
| f. Increased cost of laboratory supplies, materials, and other expenses | | 78,138,000 | | 1,269,000 |
| Subtotal | | | | 3,284,000 |
| 2. Research Management and Support: | | | | |
| a. Within grade increase | | 17,770,000 | | 309,000 |
| b. Annualization of January 2003 pay increase | | 17,770,000 | | 138,000 |
| c. January 2004 pay increase | | 17,770,000 | | 267,000 |
| d. One extra day of pay | | 17,770,000 | | 68,000 |
| e. Payment for centrally furnished services | | 7,665,000 | | 153,000 |
| f. Increased cost of laboratory supplies, materials, and other expenses | | 16,344,000 | | 260,000 |
| Subtotal | | | | 1,195,000 |
| Subtotal, Built-in | | | | 4,479,000 |

## NATIONAL INSTITUTES OF HEALTH
## National Institute of Neurological Disorders and Stroke

### Summary of Changes--continued

| CHANGES | 2003 Amended President's Budget Base | | Change from Base | |
|---|---|---|---|---|
| | No. | Amount | No. | Amount |
| B. Program: | | | | |
| 1. Research project grants: | | | | |
| a. Noncompeting | 2,001 | $767,218,000 | (116) | ($14,673,000) |
| b. Competing | 641 | 237,649,000 | 81 | 28,584,000 |
| c. SBIR/STTR | 97 | 31,388,000 | 8 | 2,785,000 |
| Total | 2,739 | 1,036,255,000 | (27) | 16,696,000 |
| 2. Research centers | 58 | 69,840,000 | 5 | 10,794,000 |
| 3. Other research | 303 | 50,369,000 | 20 | 3,739,000 |
| 4. Research training | 704 | 27,299,000 | 0 | 506,000 |
| 5. Research and development contracts | 63 | 54,500,000 | 71 | 17,563,000 |
| Subtotal, extramural | | | | 49,298,000 |
| | FTEs | | FTEs | |
| 6. Intramural research | 419 | 136,379,000 | (7) | (829,000) |
| 7. Research management and support | 190 | 41,779,000 | (3) | (443,000) |
| 8. Cancer control and prevention | 0 | 0 | 0 | 0 |
| 9. Construction | | 0 | | 0 |
| Subtotal, program | | 1,416,421,000 | | 48,026,000 |
| Total changes | 609 | | (10) | 52,505,000 |

**NATIONAL INSTITUTES OF HEALTH**
**National Institute of Neurological Disorders and Stroke**

**Budget Authority by Object**

| | FY 2003 Amended Pres. Budget | FY 2004 Estimate | Increase or Decrease |
|---|---|---|---|
| Total compensable workyears: | | | |
| Full-time employment | 609 | 599 | (10) |
| Full-time equivalent of overtime & holiday hours | 2 | 2 | 0 |
| Average ES salary | $142,400 | $146,900 | $4,500 |
| Average GM/GS grade | 10.8 | 10.9 | 0.1 |
| Average GM/GS salary | $64,825 | $67,325 | $2,500 |
| Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207) | $72,930 | $75,497 | $2,567 |
| Average salary of ungraded positions | 83,620 | 86,563 | 2,943 |
| OBJECT CLASSES | FY 2003 Amended Pres. Budget | FY 2004 Estimate | Increase or Decrease |
| Personnel Compensation: | | | |
| 11.1 Full-Time Permanent | $26,641,000 | $27,376,000 | $735,000 |
| 11.3 Other than Full-Time Permanent | 14,427,000 | 14,818,000 | 391,000 |
| 11.5 Other Personnel Compensation | 1,164,000 | 1,196,000 | 32,000 |
| 11.7 Military Personnel | 684,000 | 703,000 | 19,000 |
| 11.8 Special Personnel Services Payments | 4,685,000 | 4,919,000 | 234,000 |
| **Total, Personnel Compensation** | 47,601,000 | 49,012,000 | 1,411,000 |
| 12.1 Civilian Personnel Benefits | 10,169,000 | 10,448,000 | 279,000 |
| 12.2 Military Personnel Benefits | 480,000 | 493,000 | 13,000 |
| 13.0 Benefits for Former Personnel | 0 | 0 | 0 |
| **Subtotal, Pay Costs** | **58,250,000** | **59,953,000** | **1,703,000** |
| 21.0 Travel & Transportation of Persons | 2,657,000 | 2,710,000 | 53,000 |
| 22.0 Transportation of Things | 265,000 | 265,000 | 0 |
| 23.1 Rental Payments to GSA | 0 | 0 | 0 |
| 23.2 Rental Payments to Others | 1,460,000 | 1,489,000 | 29,000 |
| 23.3 Communications, Utilities & Miscellaneous Charges | 1,320,000 | 1,296,000 | (24,000) |
| 24.0 Printing & Reproduction | 748,000 | 707,000 | (41,000) |
| 25.1 Consulting Services | 6,215,000 | 6,839,000 | 624,000 |
| 25.2 Other Services | 10,080,000 | 10,058,000 | (22,000) |
| 25.3 Purchase of Goods & Services from Government Accounts | 86,836,000 | 90,902,000 | 4,066,000 |
| 25.4 Operation & Maintenance of Facilities | 11,328,000 | 9,328,000 | (2,000,000) |
| 25.5 Research & Development Contracts | 23,206,000 | 39,545,000 | 16,339,000 |
| 25.6 Medical Care | 110,000 | 111,000 | 1,000 |
| 25.7 Operation & Maintenance of Equipment | 5,853,000 | 5,722,000 | (131,000) |
| 25.8 Subsistence & Support of Persons | 0 | 0 | 0 |
| **25.0 Subtotal, Other Contractual Services** | **143,628,000** | **162,505,000** | **18,877,000** |
| 26.0 Supplies & Materials | 9,853,000 | 9,951,000 | 98,000 |
| 31.0 Equipment | 14,474,000 | 14,549,000 | 75,000 |
| 32.0 Land and Structures | 0 | 0 | 0 |
| 33.0 Investments & Loans | 0 | 0 | 0 |
| 41.0 Grants, Subsidies & Contributions | 1,183,763,000 | 1,215,498,000 | 31,735,000 |
| 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** | **1,358,171,000** | **1,408,973,000** | **50,802,000** |
| **Total Budget Authority by Object** | **1,416,421,000** | **1,468,926,000** | **52,505,000** |

## National Institute of Neurological Disorders and Stroke

### Salaries and Expenses

| OBJECT CLASSES | FY 2003 Amended Pres. Budget | FY 2004 Estimate | Increase or Decrease |
|---|---|---|---|
| **Personnel Compensation:** | | | |
| Full-Time Permanent (11.1) | $26,641,000 | $27,376,000 | $735,000 |
| Other Than Full-Time Permanent (11.3) | 14,427,000 | 14,818,000 | 391,000 |
| Other Personnel Compensation (11.5) | 1,164,000 | 1,196,000 | 32,000 |
| Military Personnel (11.7) | 684,000 | 703,000 | 19,000 |
| Special Personnel Services Payments (11.8) | 4,685,000 | 4,919,000 | 234,000 |
| **Total Personnel Compensation (11.9)** | **47,601,000** | **49,012,000** | **1,411,000** |
| Civilian Personnel Benefits (12.1) | 10,169,000 | 10,448,000 | 279,000 |
| Military Personnel Benefits (12.2) | 480,000 | 493,000 | |
| Benefits to Former Personnel (13.0) | 0 | 4,919,000 | 4,919,000 |
| **Subtotal, Pay Costs** | **58,250,000** | **64,872,000** | **6,622,000** |
| Travel (21.0) | 2,657,000 | 2,710,000 | 53,000 |
| Transportation of Things (22.0) | 265,000 | 265,000 | 0 |
| Rental Payments to Others (23.2) | 1,460,000 | 1,489,000 | 29,000 |
| Communications, Utilities and Miscellaneous Charges (23.3) | 1,320,000 | 1,296,000 | (24,000) |
| Printing and Reproduction (24.0) | 748,000 | 707,000 | (41,000) |
| **Other Contractual Services:** | | | |
| Advisory and Assistance Services (25.1) | 1,009,000 | 1,529,000 | 520,000 |
| Other Services (25.2) | 10,080,000 | 10,058,000 | (22,000) |
| Purchases from Govt. Accounts (25.3) | 52,064,000 | 53,117,000 | 1,053,000 |
| Operation & Maintenance of Facilities (25.4) | 11,328,000 | 9,328,000 | (2,000,000) |
| Operation & Maintenance of Equipment (25.7) | 5,853,000 | 5,722,000 | (131,000) |
| Subsistence & Support of Persons (25.8) | 0 | 0 | 0 |
| **Subtotal Other Contractual Services** | **80,334,000** | **79,754,000** | **(580,000)** |
| Supplies and Materials (26.0) | 9,840,000 | 9,938,000 | 98,000 |
| **Subtotal, Non-Pay Costs** | 96,624,000 | 96,159,000 | (465,000) |
| **Total, Administrative Costs** | **154,874,000** | **161,031,000** | **6,157,000** |

**NATIONAL INSTITUTES OF HEALTH**
**National Institute of Neurological Disorders and Stroke**

SIGNIFICANT ITEMS IN SENATE APPROPRIATIONS COMMITTEE REPORTS

The following section represents FY 2003 Congressional requirements for reports and significant items derived from Senate Report 107-216. These actions discussed below are contingent on inclusion of similar language and funding in the final FY 2003 appropriation and related reports. Additional items may be transmitted at a later date as a result of the final Conference report.

Item

***Alzheimer's disease*** – The NINDS continues to play an integral role in widening the scientific base of knowledge about Alzheimer's disease. For example, scientists have developed an antisense molecule that, when introduced intravenously, reversed learning and memory deficits in mice with an Alzheimer's-like disease. The Committee believes that the potential of antisense therapy for Alzheimer's and related disorders is promising. The Committee urges the NINDS to continue to assign a high priority to its Alzheimer's research portfolio. In addition, 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. (p. 114)

Action taken or to be taken

Alzheimer's disease (AD) continues to be a priority for NINDS, and the Institute is involved in several efforts that illustrate its commitment to a strong working relationship with NIA, NIMH, and other institutes that fund AD research. NINDS continues to participate in the trans-NIH Alzheimer's disease committee, which meets several times a year to exchange information about program activities and future plans in the area of AD. In July 2001, NINDS joined NIA in organizing and sponsoring a workshop entitled "The Biology of α-Synuclein and Lewy body Disease." This meeting brought together investigators from several different areas of neuro-degeneration research, who actively participated in an exchange of recent findings and new ideas. Based on the success of this meeting, NINDS and NIA are planning to reconvene this group, and to expand it to include investigators who received grants under special initiatives in FY 2002. NINDS is also working with NIA in the area of immunotherapy for AD, which can involve the production of antibodies that reduce the cellular and behavioral effects of the disease. NINDS continues to co-sponsor several grant awards in this area of research with NIA, and has joined NIA in the coordination of a meeting that will bring together these grantees and other experts in the field to assess the progress of basic studies and clinical trials to date; the problems associated with immunotherapy and how to overcome them; and approaches to further explore this treatment in the future. NINDS will also continue to investigate other potential therapies for AD, including the use of antisense technology and other novel interventions as appropriate.

NINDS is also committed to improving the tools for early diagnosis of AD and other degenerative disorders. The Institute has recently funded several studies on the development of improved imaging techniques in individuals with neurodegenerative diseases, including AD. One of these

projects was designed to improve PET scanning techniques, such that the relationship of cellular markers of degeneration to the clinical course of the disease can be better defined. Another study

is designed to develop a non-invasive imaging device that can be used to determine the extent of disease progression "at the bedside." In addition to these awards, NINDS will also continue to seek collaborations with other ICs, such as NIA and NIMH, to facilitate research on PET scanning and other screening tools in Alzheimer's disease.

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 the 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.114)

Action taken or to be taken

NINDS continues to work with all components of NIH, as appropriate, to expand research aimed at understanding the causes of ataxia telangiectasia and finding treatments. Ongoing studies focus on understanding how the identified gene defects lead to neurological problems, development of better animal models of A-T, elucidating the normal function of the ATM gene and protein that are altered in the disease, and developing pharmacological strategies for treating the disorder. In addition to research focused specifically on ataxia telangiectasia, NINDS has increased emphasis on cross-cutting issues critical for translating of findings from the laboratory into treatments for genetic diseases, such as ataxia telangiectasia, that affect the nervous system. In 2001, NINDS solicited proposals for grants to expand efforts to develop gene therapies in neurological diseases. In 2002, the Institute announced a broad program to foster translational research, which encourages cooperation among basic and clinical scientists, provides review tailored to this kind of research, and allows milestone-driven funding.

Item

***Batten disease*** – The Committee is disappointed with the pace of research regarding Batten disease. The Committee strongly urges the Institute to increase funding for such research by actively soliciting grant applications for Batten disease and taking aggressive steps to assure that a vigorous research program is established. (p. 114)

Action taken or to be taken

Batten disease continues to be a research priority for the NINDS. The Institute is currently sponsoring a wide range of research on Batten disease, including studies of the genes responsible for the disorder, detailed analyses of the material that accumulates in affected cells, preclinical testing of potential therapeutic interventions, and the development of cell culture and animal models of the disease. In addition to research targeted specifically to Batten disease, the Institute continues to sponsor initiatives and workshops in areas critical to progress in Batten disease as well as other disorders. These include a major program to facilitate translational research, which moves basics research findings to the point where therapies can be tested in patients, and active programs in stem cell biology, gene therapy, pediatric neuroimaging, and drug screening for

neurodegenerative diseases.

Item
***Brain Tumors*** – The Committee encourages the NINDS to continue working with the NCI to carry out the recommendations of the recently issued Report of the Brain Tumor Progress Review Group. (p. 114 )

Action taken or to be taken
As the Nation's leading supporter of biomedical research on brain and nervous system disorders, the NINDS shares with the National Cancer Institute a mutual and intense interest in advancing knowledge and understanding of brain tumors.

One of the research priorities identified in the Brain Tumor Progress Review Group's Report is to expand research on the blood-brain barrier (BBB). In its protective role, the BBB acts to hinder the delivery of many potentially important diagnostic and therapeutic agents to the brain. This presents a problem particularly in delivering therapeutic agents to specific regions of the brain, and distributing them within, and targeting them to, brain tumors. Improving our knowledge of the molecular and cellular biology of the brain vasculature, which constitutes the BBB, could lead to innovative new strategies for targeting drugs to brain tumors. In 2002, the NINDS and NCI sponsored a meeting on the BBB in central nervous system tumors, and using information from the meeting, the two Institutes plan to issue a joint program announcement to encourage research aimed at understanding the blood-brain barrier.

Item
***Duchenne muscular dystrophy*** – The Committee continues to strongly urge the NINDS to establish centers of excellence for basic and applied research in the muscular dystrophies. The Committee also urges the NINDS to coordinate with the NIAMS and the Centers for Disease Control and Prevention to develop strategic research priorities for the centers. (p.115)

Action taken or to be taken
In May 2002, NIH convened a Muscular Dystrophy Research Task Force, including scientists, physicians, and representatives of muscular dystrophy voluntary groups. The Task Force helped advise NINDS, NIAMS, and NICHD on what is needed to foster muscular dystrophy research, including what characteristics centers of excellence for muscular dystrophy research should have. In August, the NIH director, the directors of these three institutes, and NIH professional staff met with representatives of the CDC to discuss coordination of the Centers and other aspects of muscular dystrophy research. In September 2003, guided by these discussions, NIH released the request for applications (RFA-03-01) "Muscular Dystrophy Cooperative Research Centers (MDCRC)," available at: http://grants1.nih.gov/grants/guide/rfa-files/RFA-AR-03-001.html, with an application receipt date of February 24, 2003. As stated in the solicitation, the primary goal is to establish research centers, each of which will bring together expertise, infrastructure and resources focused on major questions about muscular dystrophy. The centers will promote side-by-side basic, translational, and clinical research; provide resources that can be used by the national muscle biology and neuromuscular research communities; and provide training and advice about muscle diseases for researchers and physicians who provide initial diagnosis and

treatment, including rehabilitation, care for cognitive and behavioral concerns, and therapy for

other system complications. Taken together, the centers will constitute a cohesive program, the MDCRC Program, operating under guidelines for NIH cooperative agreements.

NIH followed up in November with another solicitation, " Developmental Grants for Muscular Dystrophy Research Centers" (RFA AR-03-002), receipt date March 10, 2003, available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-03-002.html ). These grants are targeted to investigators who are not ready to establish a muscular dystrophy research center, but would like to do so eventually. The developmental grants will enable investigators to organize and integrate multidisciplinary research capacities; to enhance collaborations of basic, clinical, and behavioral science in muscular dystrophy research; and to promote cross-disciplinary research training.

Item

***Dystonia*** – The Committee continues to support the expansion of research and treatment developments regarding the neurological movement disorder dystonia, which is the third most common movement disorder after tremor and Parkinson's disease. The Committee encourages the NINDS to support additional research on both focal and generalized dystonia, and it commends the Institute for its study of the DYT1 gene and encourages expansion in this research area. Furthermore, the Institute is encouraged to support epidemiological studies on dystonia and to increase public and professional awareness of this disorder. (p.115)

Action taken or to be taken

NINDS has expanded its dystonia program and continues its efforts to further stimulate research on these disorders. The Institute worked with private dystonia groups on a January 2001 meeting, "From Genes to Function in Dystonia," and a three day "Dystonia International Symposium" held in June 2002. In August 2002, NINDS issued a program announcement (PA-02-156), "Studies into the Causes and Mechanisms of Dystonia." The purpose of this program announcement is to solicit applications for new studies on the underlying causes of human dystonia, secondary consequences of these movement disorders, and potential therapeutic strategies for treating these conditions. The Institute is also continuing its active intramural program of research on dystonia, including studies of underlying causes and early phase clinical trials of new treatment strategies.

Item

***Epilepsy*** - Epilepsy remains a major, unsolved public health problem affecting the lives of over 2.5 million Americans and their families. 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 it encourages the NINDS to expand research into the prevention, treatment, and eventual cure of epilepsy. In addition, the Committee urges the NINDS to address critical research issues related to the impact of seizures on young children, women, the elderly and those with intractable or uncontrolled epilepsy. The Committee commends the Institute on the anti-epileptic drug development program that has led to the discovery of many important anti-epileptic medications, and it encourages the Institute to further develop this program with specific research plans and goals. (p. 115)

Action taken or to be taken

NINDS is committed to both understanding the causes of, and developing effective therapies for, all forms of epilepsy, with the ultimate goal of finding a cure. The March 2000 White House - initiated Conference, "Curing Epilepsy: Focus on the Future," was jointly sponsored by NINDS, the Epilepsy Foundation, the American Epilepsy Society, Citizens United for Research in Epilepsy (CURE), and the National Association of Epilepsy Centers. It focused the epilepsy research community for the first time on the concept of a cure, which was defined as "preventing epilepsy in those at risk and no seizures, no side effects in those who develop the disorder,"

rather than just treating the symptoms of epilepsy. A major outcome of the meeting was the development of 17 research benchmarks, which will help epilepsy investigators maximize their research efforts towards the translation of basic science research findings into improved clinical therapies.

Together with the research and advocacy communities, NINDS has developed a plan for implementing the benchmarks. A central feature of this plan is the concept of stewardship, which refers to active involvement by senior well-established individuals in the epilepsy community in the status of existing and planned research that advances the goals of the specific benchmark. Stewards' responsibilities include monitoring relevant research efforts, making the research community aware of the benchmark and related funding programs or opportunities, acting as a catalyst for new initiatives, and providing regular progress reports to the NINDS. The stewards meet annually at the American Epilepsy Society meeting to discuss their activities during the past year, and to review progress made on advancing the benchmarks. Recent NINDS implementation efforts include holding workshops on "Molecular Analysis of Complex Genetic Epilepsies" (late January 2001), "Models II - Identification and Characterization of Models of Therapy Resistance and Epileptogenesis" (September 2002), "DNA Microarrays and Epilepsy" (October 2002), and "Channelopathy" (November 2002).

NINDS currently supports a varied portfolio of research projects aimed at preventing, treating, and eventually curing epilepsy, including many that have direct relevance to our understanding of seizure development in children, women, the elderly, and those individuals with intractable forms of the disease. For example, NINDS is funding a number of projects, including several new studies, investigating the possible causes and mechanisms of seizure onset in the developing brain, and the effects of early seizures on children's subsequent development (cognitive, emotional, language, and behavioral) and the risk of future development of intractable seizures in this population. The Institute also supports a number of studies of the relationship of hormonal fluctuations in females to epileptic changes in the brain (including two clinical trials). NINDS continues to support epidemiology studies of epilepsy in the elderly, with a focus on the potential differences in the efficacy and side effects of anti-epileptic medication in this population. In addition, while all epilepsy research has the potential to improve the outlook for individuals with intractable epilepsy, NINDS supports a number of projects specifically looking at severe forms of the disease, including treatment studies of intractable epilepsy in children; a new study of possible mechanism underlying drug resistant forms of epilepsy; and studies of the mechanism of, and treatments for, status epilepticus, a particularly severe uncontrolled type of epilepsy that constitutes a medical emergency. Finally, the epilepsy clinical trials portfolio is growing, and encompasses a wide range of approaches to treating the disorder. Of particular note, is a newly

funded, multi-center, randomized clinical trial to determine whether early surgical treatment of mesial temporal lobe epilepsy (MTLE) is superior to continued medication management in reducing seizure frequency and improving quality of life.
The Anticonvulsant Screening Project (ASP), a component of the former program known as the Antiepileptic Drug Development Program, is a successful public/private translational effort supported by the NINDS. Over the past 25 years, this program has collected and screened approximately 23,000 compounds for specific anti-epileptic and central nervous system effects. As a result, approximately 23 drugs have been evaluated in clinical trials, with five ultimately being made available for widespread clinical use in treating epilepsy. It is expected that in the spring/early summer of 2003 two new compounds will enter clinical investigations. Several other ASP-supported compounds are currently in various stages of clinical development. Many anticonvulsants have multiple therapeutic uses such as for neuropathic pain, anxiety, migraine, and bi-polar disorder, and current development efforts are undertaken with these potentials in mind. In addition, the Project has recently hired a new staff member to assist in the search for new anti-epileptic agents, while expanding screening activities for other related neurological diseases. Future efforts are being directed towards the development of new models to screen for agents that interrupt seizure development (epileptogenesis) and to treat highly resistant seizures, and to continue the search for treatment interventions that may prevent or cure disease.

Item
***Fragile X*** – Fragile X is a single-gene neurological disease resulting in mental disorders, cognitive impairment, and seizures. The Committee urges the NINDS to enhance its research activities on Fragile X and to include Fragile X patients in its studies of related disorders. The Committee also urges the NINDS to coordinate these efforts with other Institutes working on related activities, including the NIMH and the NICHD. (p.115)

Action taken or to be taken:
The NINDS is the primary sponsor of two new studies on Fragile X, which are also supported by NIMH and NIA. One of these studies is characterizing the relationship between Fragile X and a newly identified neurological disorder that has appeared in a substantial number of males who are genetic carriers of Fragile X-type mutations. In the second study, researchers are trying to identify genes that interact with one of the Fragile X genes using genetic screens in the fly. Other ongoing NINDS-supported studies are exploring at the cellular level how Fragile X is related to other neurological conditions, including epilepsy.

In addition to these grant awards, NINDS also collaborated with NICHD, NIMH, the NIH Office of Rare Diseases, and the Joseph P. Kennedy Jr. Foundation on a large workshop on "Emotional and Behavioral Health in Persons with Mental Retardation/Developmental Disabilities" in November 2001. This workshop was designed to identify barriers to the inclusion of people with mental retardation and developmental disabilities – including individuals with Fragile X – in federally funded research in the United States. The recommendations developed at the workshop will help increase inclusion of these individuals in research in order to promote evidenced-based treatment for this population.

Item
***Mucopolysaccharidosis (MPS)*** – The Committee commends the NINDS for sponsoring a

scientific conference focusing on central nervous system issues and the barriers to and development of effective therapies for MPS disorders, and urges the NINDS to solicit investigator proposals resulting from the findings of the conference. The Committee also encourages the NINDS, in collaboration with the NIDDK and the NICHD, to support current MPS research and use all available mechanisms to further stimulate and enhance efforts to better understand and treat MPS disorders. (p.115)

Action taken or to be taken

NINDS, the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), the National Institute of Child Health and Human Development (NICHD), and the NIH Office of Rare Diseases, working with voluntary health organizations, co-sponsored the workshop, "The Mucopolysaccharhidoses: Therapeutic strategies for the central nervous system," held on September 24-25, 2002. The workshop brought together basic scientists, clinicians, and family members confronting these diseases. NINDS is continuing to work to stimulate research on the mucopolysaccharidoses. In addition to research focused on these diseases, workshop participants highlighted the importance of several cross-cutting areas of research as crucial for progress against the mucopolysaccharidoses, as well as for many other neurological disorders. NINDS is actively engaged in expanding programs in these critical areas, which include gene therapy for the nervous system, neural stem cells, access to transgenic mouse models, the blood-brain barrier, and pediatric neuroimaging.

Item

***Neurofibromatosis*** – Neurofibromatosis (NF) is a genetic disorder of the nervous system that causes tumors to grow along nerves anywhere on or in the body. The Committee is aware that recent advances in research have linked NF to cancer, brain tumors, learning disabilities and heart disease, and it urges the NINDS to expand its NF basic and clinical research portfolio. (p. 115)

Action taken or to be taken

The NINDS engages in a broad range of activities to stimulate innovative research in NF. The NINDS continues to support research on the genetic causes of NF and the molecular and cellular events that underlie the development of NF-associated tumors. In FY 2002, the NINDS funded new studies to investigate the genetic basis for the dramatic variability in NF symptoms. The NINDS also provides multiple forums for researchers, clinicians, and patient groups to identify critical gaps in our understanding of NF, and to develop strategies and collaborations to address these gaps. Most notably, the NINDS was the lead NIH institute (through a competitive grant mechanism) in supporting the June 2002 meeting of the National Neurofibromatosis Foundation International Consortium for the Molecular and Cell Biology of NF1 and NF2. In addition to supporting research and meetings focusing specifically on NF, the NINDS sponsors initiatives on broader topics that will be critical to developing therapies for NF. These include a major program to facilitate the translation of basic research findings into therapies that can be tested in clinical trials and an active program in gene therapy.

Item

***Stroke*** – The Committee continues to regard research into the causes, cure, prevention, treatment and rehabilitation of stroke as one of the Nation's top priorities. The Committee commends the NINDS for convening a Stroke Progress Review Group, consisting of researchers, clinicians,

pertinent organizations and advocacy groups. This Group crafted a report that will serve as a blueprint for a long-range strategic plan on stroke research.

The Committee is concerned that funding for stroke research over the years may not have kept pace with the scientific opportunities and the number of Americans afflicted with stroke. The Committee encourages the NINDS to dedicate more resources to stroke research and to expand its stroke education program. The Committee also encourages the NINDS to expand its research efforts into the utility of PET scans of the brains of stroke victims to determine whether brain tissue damage from stroke may be reversible. (p. 116 )

Action taken or to be taken

NINDS continues to place a high priority on stroke-related research. The NINDS stroke program ranges from basic investigation of stroke mechanisms through large studies of risk factors and clinical trials aimed at prevention or treatment. Interventions under investigation include drugs, surgery, vitamins, physical therapy, and psychosocial modalities Research is also targeted to special issues of stroke in geographic regions ("the stroke belt"), minority populations, women, and children.

Several new efforts are planned or underway. The Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS) will help develop rapid diagnosis and therapeutic interventions. With regard to genetics, stroke is among the disorders targeted in the new NINDS Human Genetic Repository, and the Institute will provide administrative supplements to ongoing clinical trials to encourage participation. The Stroke Prevention/Intervention Research Program (SPIRP) will address issues related to minority populations and the "stroke belt." NINDS held a November 2002 workshop focused on stroke health disparities, and is planning meetings on intracerebral hemorrhage, and on primary prevention to help guide further efforts in those areas. The blood-brain barrier was highlighted as a priority of the Stroke PRG, the Brain Tumor PRG, and other NINDS strategic and disease specific planning groups; a solicitation will address needs in this critical area of research. The NINDS intramural stroke program continues its outstanding research efforts. For example, intramural scientists are pursuing a unique but promising vaccine strategy for stroke prevention. The 24-hour acute stroke research program in diagnosis and treatment at Suburban Hospital in Bethesda, Maryland, is ongoing, with plans to replicate this program in another medical facility, particularly one serving predominantly inner city minority populations. The Institute is also enhancing its efforts, in cooperation with private groups, to improve public awareness of stroke and the need for rapid treatment. Several Federal health agencies, including NINDS and NHLBI at the NIH, have partnered with the American Heart Association to speed progress toward the heart disease and stroke goals set forth in Healthy People 2010, a national health promotion and disease prevention initiative. The Federal agencies and the American Heart Association will work to accomplish these goals through focused initiatives including: research; population- and community-based public education and health promotion programs; media-based public awareness campaigns about the warning signs and symptoms of heart attack and stroke; and promoting professional education and training, including co-hosting of national conferences and the dissemination of "best practices."

In July 2001, the NINDS held a meeting of 150 nationally and internationally recognized stroke experts, called the Stroke Progress Review Group (PRG), who were to identify and set research

priorities. The attendees were divided into panels in fifteen topic areas, including neuroimaging. The imaging panel defined research needs and priorities in this growing and fast-moving field that includes computerized axial tomography (CT) scans, positron emission tomography (PET), proton magnetic resonance imaging (MRI), functional MRI (fMRI). The report of the PRG has been published, and the NINDS staff have identified ongoing research that addresses the priorities set by the PRG. With the PRG members, NINDS will be identifying areas that need additional study and outlining steps to address those gaps and needs; the appropriate use of PET imaging to evaluate stroke will be examined in that process.

Item

***Traumatic brain injury (TBI)*** – There are at least 1.5 million people who sustain a traumatic brain injury (TBI) annually, and at least 5.3 million people who live with a disability as a result of TBI. The Committee urges the NINDS to expand bench science research on the mechanisms of this disorder and to begin translational research into clinical settings. (p. 116)

Action taken or to be taken

NINDS research on traumatic brain injury (TBI) focuses on understanding the mechanisms and consequences of injury to the brain. Major emphases are placed on the prevention of secondary damage, preservation of neurons and neural circuits, and regeneration and plasticity. NINDS grantees are exploring a variety of interventions to limit damage resulting from trauma and to promote repair of the damaged nervous system, as well as conducting research on ways to promote recovery of cognitive and language function following brain injury. Basic science research on TBI is an ever-expanding field, and as new mechanisms of injury and possible interventions are uncovered, NINDS will continue to evaluate approaches that can enhance and expand this research further.

In order to stimulate translational research in all areas of neurological disease, including TBI, NINDS has recently released several program announcements intended to encourage applications focused on the development and refinement of new therapeutics in the pre-clinical setting. The program will facilitate the effective review and research administration of translational research projects, and will accelerate the translation of discoveries in basic research to treatment in the clinic. Cooperative agreements for large studies, mentored research scientist development awards, and smaller awards for exploratory/developmental projects are all available through this program. Although these grant announcements were only released in July 2002, NINDS has already received an enthusiastic response from the research community about the need for such a program.

In addition to the NINDS program of basic research in TBI, and its new investments in translational research, the Institute is also supporting many clinical studies in the field. These include investigations of steroids, immunosuppressives, hyperbaric oxygen, hypothermia and magnesium for treating TBI. Other clinical studies are designed to more accurately assess cognitive abilities after TBI, and to evaluate possible strategies for rehabilitation.

## NATIONAL INSTITUTES OF HEALTH
## National Institute of Neurological Disorders and Stroke

**Authorizing Legislation**

| | PHS Act/ Other Citation | U.S. Code Citation | 2003 Amount Authorized | 2003 Amended President's Budget | 2004 Amount Authorized | 2004 Budget Estimate |
|---|---|---|---|---|---|---|
| Research and Investigation | Section 301 | 42§241 | Indefinite | $1,389,122,000 | Indefinite | $1,441,121,000 |
| National Institute of Neurological Disorders and Stroke | Section 41B | 42§285b | Indefinite | | Indefinite | |
| National Research Service Awards | Section 487(d) | 42§288 | a/ | 27,299,000 | b/ | 27,805,000 |
| Total, Budget Authority | | | | 1,416,421,000 | | 1,468,926,000 |

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.
b/ Reauthorizing legislation will be submitted.

## 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/ |
|---|---|---|---|---|
| 1995 | $630,443,000 2/ | $626,471,000 | $628,801,000 | $627,726,000 3/ |
| Rescission | | | | (647,000) |
| 1996 | 648,255,000 2/ | 681,534,000 | 639,152,000 2/ | 681,534,000 |
| Rescission | | | | (599,000) |
| 1997 | 671,148,000 2/ | 725,478,000 | 683,721,000 2/ | 726,746,000 4/ |
| 1998 | 722,712,000 2/ | 763,325,000 | 781,351,000 | 780,713,000 |
| 1999 | 815,649,000 2/5/ | 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 | | | |
| 2004 | 1,468,926,000 | | | |

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
3/ Excludes enacted reductions of $321,000 for procurement, $33,000 for SLUC, and $221,000 for the limitation on 1% Bonus Pay.
4/ Excludes enacted administrative reduction of $339,000

## NATIONAL INSTITUTES OF HEALTH
## National Institute of Neurological Disorders and Stroke

### Detail of Full-Time Equivalent Employment (FTEs)

| OFFICE/DIVISION | FY 2002 Actual | FY 2003 Amended Pres. Budget | FY 2004 Estimate |
|---|---|---|---|
| Office of the Director | 67 | 71 | 69 |
| Division of Extramural Activities | 114 | 119 | 118 |
| Division of Intramural Research | 424 | 419 | 412 |
| Total | 605 | 609 | 599 |
| FTEs supported by funds from Cooperative Research and Development Agreements | (3) | (2) | (2) |

| FISCAL YEAR | Average GM/GS Grade |
|---|---|
| 2000 | 10.4 |
| 2001 | 10.3 |
| 2002 | 10.7 |
| 2003 | 10.8 |
| 2004 | 10.9 |

**NATIONAL INSTITUTES OF HEALTH**
**National Institute of Neurological Disorders and Stroke**

**Detail of Positions**

| GRADE | FY 2002 Actual | FY 2003 Amended Pres. Budget | FY 2004 Estimate |
|---|---|---|---|
| ES-6 | 1 | 1 | 1 |
| ES-5 | 0 | 1 | 1 |
| ES-4 | 3 | 2 | 2 |
| ES-3 | 0 | 0 | 0 |
| ES-2 | 0 | 0 | 0 |
| ES-1 | 0 | 0 | 0 |
| Subtotal | 4 | 4 | 4 |
| Total - ES Salary | $552,800 | $572,260 | $592,403 |
| GM/GS-15 | 42 | 43 | 43 |
| GM/GS-14 | 51 | 53 | 53 |
| GM/GS-13 | 54 | 54 | 52 |
| GS-12 | 69 | 71 | 71 |
| GS-11 | 56 | 58 | 55 |
| GS-10 | 7 | 5 | 5 |
| GS-9 | 48 | 48 | 46 |
| GS-8 | 29 | 30 | 29 |
| GS-7 | 42 | 41 | 40 |
| GS-6 | 14 | 14 | 13 |
| GS-5 | 4 | 6 | 6 |
| GS-4 | 14 | 14 | 14 |
| GS-3 | 4 | 3 | 3 |
| GS-2 | 3 | 2 | 2 |
| GS-1 | 2 | 2 | 2 |
| Subtotal | 439 | 444 | 434 |
| Grades established by Act of July 1, 1944 (42 U.S.C. 207): | | | |
| Assistant Surgeon General | 0 | 0 | 0 |
| Director Grade | 4 | 4 | 4 |
| Senior Grade | 4 | 3 | 3 |
| Full Grade | 0 | 0 | 0 |
| Senior Assistant Grade | 1 | 1 | 1 |
| Assistant Grade | 0 | 0 | 0 |
| Subtotal | 9 | 8 | 8 |
| Ungraded | 190 | 190 | 190 |
| Total permanent positions | 452 | 456 | 446 |
| Total positions, end of year | 642 | 646 | 636 |
| Total full-time equivalent (FTE) employment,end of year | 605 | 609 | 599 |
| Average ES level | ES-4 | ES-4 | ES-4 |
| Average ES salary | $138,200 | $142,400 | $146,900 |
| Average GM/GS grade | 10.7 | 10.8 | 10.9 |
| Average GM/GS salary | $62,325 | $64,825 | $67,325 |