FISCAL YEAR 2003

Justification of Appropriation

Estimates

National Institutes of Health

National Institute of Neurological Disorders and Stroke

January 25, 2002

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

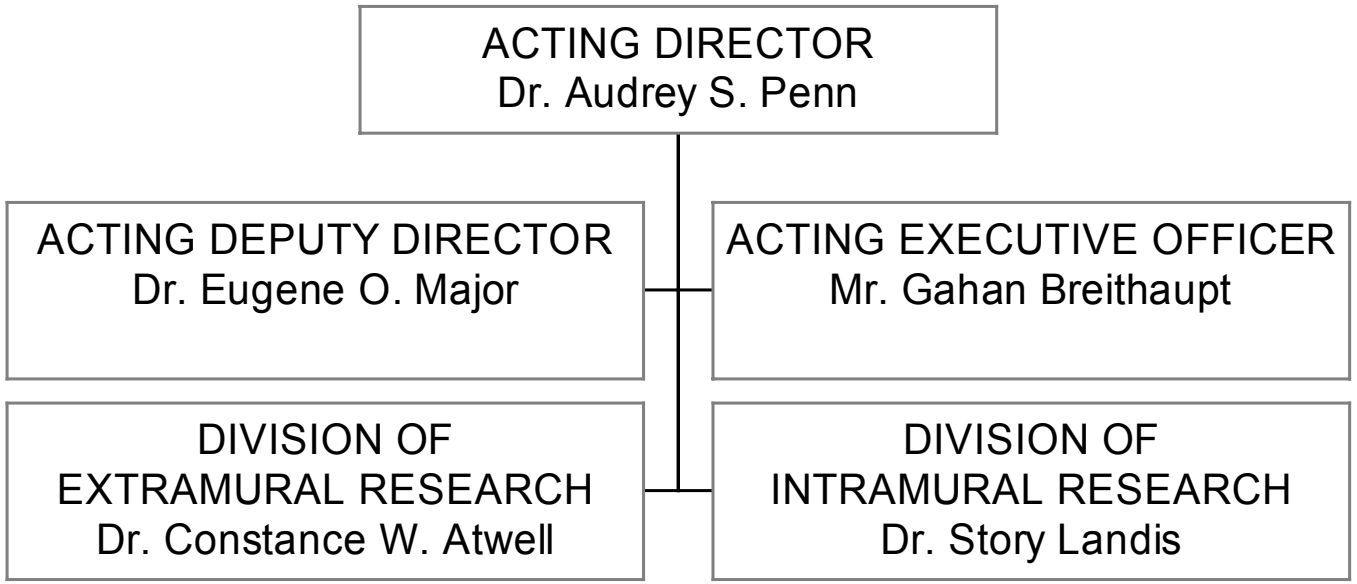
National Institute of Neurological Disorders and Stroke

FY 2003 Budget — Page No.

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, [$1,328,188,000] *$1,416,780,000.*

[Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2002 as enacted by the Consolidated Appropriations Act, 2002 (P.L. 107-116)]

National Institutes of Health

National Institute of Neurological Disorders and Stroke
Amounts Available for Obligation 1/

Source of Funding	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
Appropriation	$1,176,482,000	$1,328,188,000	$1,412,793,000
Enacted Rescission	(383,000)	(408,000)	---
Subtotal, Adjusted Appropriation	1,176,099,000	1,327,780,000	1,412,793,000
Comparable adjustment for legislative proposal for accrued retirement costs	3,572,000	3,868,000	3,987,000
Real transfer to:			
Other HHS Agencies through Secretary's one-percent transfer authority	(223,000)	---	---
Real transfer to HHS for the Office of Human Research Protection	(245,000)	---	---
Comparative transfer from:			
Office of the Director for the Academic Research Enhancement Award program	1,166,000	0	
National Cancer Institute for research activities	---	---	26,612,000
Comparative transfer to:			
National Institute of Biomedical Imaging and Bioengineering	(4,665,000)	(0)	
Subtotal, adjusted budget authority	1,175,704,000	1,331,648,000	1,443,392,000
Unobligated balance, lapsing	(40,000)	---	---
Total obligations	1,175,744,000	1,331,648,000	1,443,392,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2001 - $5,576; FY 2002 - $5,583; FY 2003 - $5,586
Excludes $129,718 in FY 2001 and $200,000 in FY 2002 for royalties.

Justification

National Institute of Neurological Disorders and Stroke

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

Budget Authority:

	2001 Actual	2002 Appropriation	2002 Current Estimate	2003 Estimate	Increase or Decrease
Current Law BA	$1,172,132,000	$1,328,188,000	$1,327,780,000	$1,439,405,000	$111,625,000
Accrued Costs	$3,572,000	$3,868,000	$3,868,000	$3,987,000	$119,000
Proposed Law BA	$1,175,704,000	$1,332,056,000	$1,331,648,000	$1,443,392,000	$111,744,000
FTE	589	618		616	-2

This document provides justification for the Fiscal Year 2003 activities of the National Institute of Neurological Disorders and Stroke (NINDS), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2003 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR).

The President's appropriations request of $1,443,392,000 for this account includes current law adjusted by assuming Congressional action on the proposed Managerial Flexibility Act of 2001.

INTRODUCTION

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disease through research on the healthy and diseased brain, spinal cord, and nerves of the body, which together make up our nervous system. The intricacy of the brain is awesome, its mechanisms are elusive, and an extraordinary variety of diseases affect the nervous system. Furthermore, the brain and spinal cord are difficult to access, sensitive to intervention, and reluctant to regenerate following damage. For these reasons neurological disorders often defy the best efforts of medicine, even in the modern era.

However, the last decade has brought remarkable progress, with the first treatments—albeit still far from adequate— for acute stroke and spinal cord injury, new immune therapies that ameliorate symptoms and slow the progression of multiple sclerosis, and increased drug and surgical options for Parkinson's disease, epilepsy and chronic pain. Molecular genetics and brain imaging are augmenting clinicians' insight to diagnose the bewildering array of diseases and

guide therapy. Continuing progress in preventing stroke and birth defects is having a major impact on public health. Perhaps most encouraging, an unprecedented variety of new treatments and prevention strategies are under development. These include drugs that home in on the molecular processes that cause disease, stem cell therapies that replace lost nerve cells, neural prostheses that read control signals directly from the brain, vaccines that target neurodegeneration, implantable electrical stimulators that compensate for brain circuits unbalanced by disease, vectors to repair or replace defective genes, and behavioral interventions that encourage the brains latent capacity to repair itself. It would be a disservice to patients and families to promise when cures will become available, because medical progress is notoriously difficult to predict. Yet, researchers are cautiously optimistic that we are entering an era when preventing or curing most nervous system disorders and even repairing the damaged nervous system will become commonplace.

An extraordinary range of disorders affect the nervous system, including trauma, infections, toxic exposure, birth defects, degenerative diseases, tumors, gene mutations, systemic illness, vascular events, nutritional deficiencies, and adverse effects of essential treatments. Some neurological disorders, like stroke, chronic pain conditions, dementias, and traumatic brain injury, are among the leading causes of death and disability in the nation. Others, such as epilepsy, spinal cord injuries, multiple sclerosis, Parkinson's disease, muscular dystrophies, autism, cerebral palsy, and peripheral nerve disorders, are common enough to be familiar to most Americans. But there are also hundreds of less common or rare diseases, unheard of by most people until a family member is affected–ataxia telangiectasia, Canavan disease, Batten disease, Friedreich's ataxia, progressive supranuclear palsy, to name just a few. These, too, collectively take an enormous toll. Rare diseases may have a disproportionate impact on public health, as is the case for Creutzfeldt-Jakob disease (CJD), which raises concerns about the safety of therapeutic blood products, and research yields clues to more common ailments, so these problems merit special attention even beyond their individual impact.

Progress against the many neurological diseases also requires a broad spectrum of research from laboratory studies of molecules, cells, and animals, through clinical studies that involve human patients. Basic science is the wellspring of future advances against disease, and NINDS attends to diverse areas of science that have a potential impact on neurological disease, from molecular biology to cognitive and behavioral studies. A wide range of technologies also demand attention, from microarrays that allow monitoring activity of thousands of genes, through electronics, computer technologies, high-throughput drug screening, and imaging that reveals brain activity and chemistry. NINDS must also focus efforts from diverse medical disciplines and clinical research specialties, including neurology, surgery, cancer, immunology, infectious diseases, imaging, and emergency medicine. Clinical laboratory studies reveal underlying processes that go wrong in disease. Translational research bridges the gap from basic studies to interventions that can safely be tested in patients. Finally, randomized, controlled clinical trials are the gold standard for testing whether treatments are safe and effective.

NINDS focuses resources on diseases for which the science seems close to helping people, without abandoning work on problems about which we have as yet few clues. The Institute seeks to expedite even incremental improvements in the quality of life for people now confronting

neurological problems, while continuing long-term efforts toward real cures and prevention. When appropriate NINDS supports targeted, centrally-coordinated efforts, but without sacrificing the unsolicited research proposals that engage the collective ingenuity of the scientific community and stimulate innovation. The Institute attends to disorders that impose special burdens on children, on women, on minorities, and on particular geographic regions of the United States. Because diseases do not respect the neat boundaries that divide Institutes and Agencies, NINDS works with other components of the government, within and outside NIH, and remains cognizant of the broader research and health care context, recognizing what government can do best, what is in the province of the private sector, and how public and private organizations can work together. The Institute supports today's researchers while training the next generation and attending to the high-technology infrastructure that will be necessary in the future. Finally, NINDS plans for future uncertainties.

PARKINSON'S DISEASE

Congress, in FY 2000 Conference Report language, directed NIH to develop a Parkinson's disease research agenda for the next five years. At a January 2000 workshop, intramural, extramural, and industry scientists, representatives from several Parkinson's disease advocacy groups, and ethicists held intensive discussions which formed the basis of the "NIH Parkinson's Disease Research Agenda." The Agenda encompasses research from basic studies to understand the normal brain functions disrupted by this disease through clinical studies of therapeutic strategies, including drugs, cell replacement, gene manipulations, and surgery.

NINDS activities to carry out the Agenda, together with the extensive research on Parkinson's already underway, represent the most aggressive effort the Institute has ever undertaken against any disease. The Institute publicized the Agenda widely in the scientific community, and investigator initiated projects make up the greatest share of research toward most Agenda goals. The Institute, cooperating with other components of NIH and increasingly with private groups, is augmenting those efforts with activities targeted to specific objectives of the Agenda. The following lists illustrate the extent of those activities. The enumeration includes a few items released prior to the Agenda meeting or not targeted solely to Parkinson's disease, but all are directly responsive to needs highlighted by the Agenda.

Grant solicitations:

- The role of the environment in Parkinson's disease and career development awards in the role of the environment in Parkinson's disease [led by NIEHS]
- Consortium on deep brain stimulation for the treatment of Parkinson's disease
- Function of synaptic proteins in synaptic loss and neurodegeneration
- Role of parkin and related proteins in Parkinson's disease
- Mitochondrial function in neurdegeneration
- Gene discovery for neurological and neurobehavioral disorders
- Parkinson's disease neuroprotection trial–coordinating and statistical centers
- Parkinson's disease neuroprotection trial–clinical centers
- Biology of non-human stem cells in the environment of the nervous system

- Gene therapy for neurological disorders
- Fast track grants for Parkinson's disease research
- Technology development for safe and effective deep brain stimulation
- Mechanisms of action of deep brain stimulation

Contract solicitations:
- High throughput screening facility for neurodegenerative disease
- DNA repository for human genetics

Workshops and other meetings:
- Parkinson's disease epidemiology workshop [led by NIEHS]
- The role of the environment in Parkinson's disease [led by NIEHS]
- Workshop on therapeutic opportunities in Parkinson's disease
- Gene therapy in neurological disorders [partly focused on Parkinson's disease]
- NINDS teaching workshop on the neurobiology of Parkinson's disease at the Society for Neuroscience Annual Meeting
- Workshop on the cognitive and emotional aspects of Parkinson's disease
- Synuclein and cortical Lewy bodies associated with dementia in Alzheimer's disease, Lewy body disease and Parkinson's disease.
- Udall Centers meetings
- Parkinson's Disease Implementation Committee meetings

Supplement programs: Within present regulations NIH can award supplements to existing grants more quickly that it can award new grants, if the subject of research is close enough to the aims of grants that have already undergone appropriate review and approval. NINDS supplement programs target:
- Expanding ongoing NINDS grants to include research on Parkinson's disease
- Screening FDA-approved compounds for use against neurodegenerative diseases
- Supporting DNA microarray analysis
- Providing necessary infrastructure

Udall Centers: In the year prior to the Agenda, NINDS began funding of 11 Morris K. Udall Parkinson's Disease Research Centers of Excellence. The Udall Centers carry out research activities in all areas of the Agenda and meet regularly to discuss unpublished findings and arrange collaborative efforts. NINDS has supplemented centers to carry out additional research responsive to Agenda needs. Among the topics that are the focus of supplements:
- High-throughput screening to find candidate compounds for Parkinson's disease drugs
- Sharing of biological reagents relevant to Parkinson's disease
- Parkinson's disease genes in isolated populations and in minority racial and ethnic groups
- Parkinson's disease brain banking

The expanded NINDS Neurodegeneration cluster leads the effort and calls upon expertise throughout NIH in areas such as clinical genetics, gene therapy, deep brain stimulation technology, cognitive and emotional health, stem cell research, and clinical trials. To help focus efforts, NINDS formed a Parkinson's Disease Implementation Committee (PDIC) which includes

representatives of Parkinson's disease advocates and of the scientific community, as well as NIH staff. The Institute has also created a website that tracks agenda activities for the public and the scientific community.

To move from identifying an Agenda objective to fulfilling that need, NIH and outside scientists must write solicitations, prepare and peer review grant proposals, and, most importantly, carry out the research itself. Given these requirements, too little time has passed to judge how effective Agenda efforts have been, or to disentangle research advances from the results of the extensive ongoing NIH efforts against Parkinson's disease. However, a few examples of recent findings and ongoing efforts illustrate the rapid pace of research.

Genetics: Genetic studies of Parkinson's disease are advancing on several fronts. Studying less common inherited forms is leading to better understanding of all types of Parkinson's disease because similar underlying processes are responsible. An NIH workshop led to the first discovery, in 1997, of a gene defect that can cause Parkinson's disease–a mutation in the gene for the protein *alpha-synuclein*. Japanese investigators then discovered that defects in a gene called *parkin* are responsible for a rare juvenile form of Parkinsonism. This year Udall center scientists firmly linked parkin to "typical" Parkinson's disease and, surprisingly, also linked some cases of Parkinson's to defects in the genes SCA2 and SCA3, which cause spinocerebellar ataxias, another type of neurodegenerative disorder. Clinical-genetic studies have also identified, for the first time, normal variations of other genes, such as the gene Tau, that may affect susceptibility to Parkinson's. In FY01, NINDS awarded supplements for this work to Udall centers and issued a request for applications to stimulate work in this area.

Cell biology: The proteins synuclein and parkin were both first associated with Parkinson's disease by studying inherited forms of the disorder. Follow up studies are revealing how these proteins come into play in non-inherited Parkinson's and uncovering the chain of events that links the two proteins in the disease process. A new study shows that parkin, which is part of the normal cellular process that tags cellular proteins for disposal and recycling, marks synuclein molecules for this process in healthy nerve cells. Abnormal aggregations of proteins, perhaps reflecting defective degradation processes, are a hallmark of several neurodegenerative diseases. Indeed synuclein aggregations are associated with Alzheimer's and other forms of dementia as well as Parkinson's. Finding ways to prevent these accumulations may be an strategy for preventing the progression of these diseases and research is underway to find ways to do this. In FY01 NINDS issued two requests for grant applications in this area of research and, with NIA, sponsored a workshop on synuclein in neurological disease.

Animal models: Animal models of neurological disorders are essential for understanding what causes disease and for testing new treatments. Scientists recently reported that chronic administration of the pesticide rotenone induces the major features of Parkinson's disease in rats. Rotenone apparently acts on mitochondria, the energy factories of the cell. In other studies, scientists are building on gene findings to develop mouse and even fruitfly models of Parkinson's disease. In FY01 NINDS solicited grants to study the role of mitochondria in neurodegeneration, supplemented work on further development of animal models for Parkinson's disease, and began a process to facilitate exchange of information among scientists about the various animal models.

Drug therapies: In the 1950s scientists discovered that dopamine is a neurotransmitter in the brain, leading to recognition that dopamine loss is critical in Parkinson's disease. A decade later introduction of the drug levodopa, which helps replenish dwindling supplies of dopamine, revolutionized treatment. However, levodopa does not slow the underlying death of nerve cells and ultimately fails as the disease progresses. NINDS is continuing its efforts to refine current therapies for Parkinson's, including, for example, a large clinical trial to determine when in the course of disease levodopa therapy should begin and, working with the Veterans' Administration, a clinical trial that will compare best medical therapy with surgical interventions. The Institute is also moving toward clinical trials of neuroprotectants– drugs that actually slow or stop the progression of the disease. The Institute has solicited applications for coordinating and statistical centers and more than 40 clinical centers to participate in clinical trials of neuroprotective drugs. NINDS is actively seeking candidate drugs for testing from academic researchers and industry. To expedite drug development for Parkinson's disease more broadly the Institute supplemented a Udall Center to apply high throughput screening, a technology which uses robotics to rapidly test large numbers of drugs. In parallel efforts, the Institute has funded researchers to test drugs already approved by the FDA for other purposes and is developing a contract center for high throughput screening of drugs for neurodegenerative disorders.

Neurotrophic factors and gene therapy: Short term experiments in animal models have suggested that the natural "neurotrophic" (growth and survival) brain chemical GDNF might protect dopamine nerve cells from dying in Parkinson's disease. However, this goal has been thwarted by the difficulty of delivering this large molecule to the brain. A team of scientists have now adapted a type of virus, called a lentivirus, to carry the gene for GDNF into brain cells, along with signals that prompt cells to turn on the gene. In non-human primate models of Parkinson' disease the lentivirus GDNF gene therapy reduced degeneration of dopamine cells and alleviated movement control symptoms. In FY01 NINDS held a workshop on gene therapy, dedicated in part to Parkinson's disease and issued a follow-up request for grant applications. Investigators from that meeting formed a consortium on gene therapy for Parkinson's disease.

Cell replacement therapies: Nerve cells that produce the neurotransmitter dopamine die in Parkinson's disease. Replacing these cells may be the best hope for people with advanced disease. This year the first controlled clinical trial to test fetal tissue transplantation showed that the problems outweighed the benefits for the particular procedure used. However, the trial provided proof in principal for cell therapy -- transplanted cells survived, produced dopamine, and altered movement control. Another clinical trial is underway to test a different fetal tissue transplant procedure. Experiments in rodent models of Parkinson's suggest that stem cells may ultimately provide better methods for cell replacement therapy and NINDS is funding primate studies as a step toward human trials. The Institute's extensive studies on adult human stem cells and animal stem cells are continuing to produce results that are potentially useful for Parkinson's disease, including recent Intramural progress in efficiently generating dopamine nerve cells from animal stem cells. NINDS, together with other components of NIH, is offering a series of solicitations to encourage scientists to carry out the fundamental studies of stem cell biology that are necessary for this therapeutic strategy to move forward and is working with the FDA toward meeting requirements for human trials.

Non-motor symptoms: People coping with Parkinson's must confront a wide range of symptoms beyond disruption of movement control. These include dementia, sleep disturbances, depression, swallowing problems, sexual dysfunction, and cardiovascular disturbances. Symptoms suggest that some of these non-motor symptoms involve malfunction of the sympathetic nervous system, which is part of the body's "fight-or-flight" stress response network and relies upon the neurotransmitter norepinephrine, a chemical closely related to dopamine. Last year NINDS intramural researchers using the imaging technique positron emission tomography (PET) discovered that most patients with Parkinson's disease lose sympathetic norepinephrine nerve terminals in the heart. Researchers are now investigating whether loss of sympathetic nerve terminals also occurs in other parts of the body and may contribute to other non-motor symptoms of Parkinson's disease.

These highlights can only suggest the extent of research that is underway in all areas of the Agenda. Other promising recent results or ongoing studies, for example, focus on environmental and lifestyle influences, interrupting the "cell suicide" process that kills nerve cells, the mechanisms and effectiveness of chronic deep brain stimulation, ethics of surgical therapies, and early indicators of Parkinson's. The NINDS Parkinson's Disease Research Web site gives more details at: http://www.ninds.nih.gov/parkinsonsweb/index.htm.

The Agenda highlighted the extent of opportunities available for research against Parkinson's disease. The research encompasses many scientific areas and technologies, spans the spectrum from basic science through large clinical trials, includes efforts to refine existing therapies and to develop new approaches on the frontiers of medicine, and relies upon both traditional investigator initiated grants and more centrally directed research.

UNDERSTANDING THE NORMAL NERVOUS SYSTEM AND ITS DISORDERS

Many aspects of the nervous system and its disorders still elude our understanding. We do not know what triggers neurodegenerative disorders such as Parkinson's, ALS, and Alzheimer's, and why only certain nerve cells die in each disorder. Similar gaps cloud our understanding of epilepsy, persistent pain, multiple sclerosis, and other diseases. Moving from finding defective genes to cures for inherited neurological disorders still defies the best efforts. Understanding why brain cells are so reluctant to repair damage and overcoming those limitations are also challenges for the future. Perhaps underlying all, understanding of how the normal brain controls movement, emotions, perception, thinking and memory is just now emerging. Yet, in recent years there has been significant progress toward solving all of these critical questions. It is a testament to the complexity of the brain that we have learned so much, but there is still so much more to learn.

Today's promising new therapeutic strategies–stem cells to replace lost nerve cells, "neuroprotectants" to prevent damage to the brain, gene therapies, deep brain stimulation to restore unbalanced electrical activity, and drugs designed to interrupt the cascade of processes that lead to nerve cell death–all arose from fundamental studies about the normal nervous system, often begun decades ago. Because the same research holds the key for many neurological disorders, basic studies are an essential foundation for NINDS to confront the overwhelming variety of diseases within its mission. Because the path from basic science to practical

application is long and unpredictable, industry and private groups are unlikely to finance this work, which heightens the importance of the NINDS role.

Although it is tempting to think of a straight path from understanding the normal nervous system, to discovering what goes wrong in disease, and on to treatment and prevention, the reality has always been much more complex. There is a continuing interplay at all levels. Just as early studies of brain injuries enabled neurologists to decipher the basic functional plan of the brain, gene findings about diseases are helping today's scientists understand how the normal brain works at the level of cells and molecules. Landmark genetic results are balanced by equally exciting findings about plasticity, the brain's capacity to change in response to experience, the environment, and disease. A few recent findings illustrate progress in understanding the nervous system and its disorders:

Nerve cell signaling: Nerve cells communicate with one another across junctions called synapses via chemical messengers called neurotransmitters and specialized detectors called neurotransmitter receptors. Most drugs for nervous system disorders act through these chemical signaling systems. For example drugs target dopamine neurotransmission in Parkinson's disease, GABA in epilepsy, acetylcholine in Alzheimer's, serotonin in depression, and "endogenous opioids" in pain. Scientists are still unraveling the complex players in this chemical signaling system. One new avenue arises from studies of marijuana, which affects the brain by its resemblance to natural neurotransmitters called endogenous cannabinoids. Until recently scientists were at a loss to explain the functions of cannabanoids in the brain, but new studies reveal that cannabinoids carry messages in the reverse direction of the usual flow of signaling across synapses, perhaps helping to fine-tune future signals sent by neighboring nerve cells. Drugs based on the cannabanoid system are promising candidates for a variety of disorders.

Glial cells: Glial cells outnumber nerve cells in the human brain by ten to one. For many years glia were regarded as passive supporting cells, but we now know that glia release chemicals crucial for the growth and survival of nerve cells, regulate the concentration of signaling molecules in the fluid that surrounds brain cells, guide growing nerve fibers, and react as a first line of defense against disease and trauma. Most recently scientists have found in cell culture that glial cells help govern information processing abilities of the brain by regulating the number of synapses that form between nerve cells and by maintaining healthy synaptic connections. Glia have always had a negative side too, because "gliomas" are the most common and serious brain tumors. New evidence implicates glia also in many persistent pain states, such as the painful neuropathy that often accompanies AIDS. Understanding glial cells is likely to have implications for treating a wide variety of disorders in the future.

Genes and the brain: Far more genes are active in the nervous system than in any other tissue– more than half of our genes probably play important roles in the brain. Research has already identified the gene defects responsible for more than 200 neurological disorders, most recently forms of muscular dystrophy, epilepsy, Alexander's disease, Parkinson's disease and ALS. Furthermore, 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. Molecular genetics is also a scalpel to dissect processes in

the normal brain. This year, for example, by switching on or off genes in the mouse brain, scientists continued to unravel how molecules, such as calcium/calmodulin-dependent protein kinase IV (CaMKIV) and protein kinase A (PKA), underlie the fundamental process of memory.

Genes and brain tumors: Brain tumors, like all forms of cancer, are genetic diseases—not in the sense that they are inherited but because the uncontrolled growth reflects defects in genes that influence the cells' behavior. The Brain Tumor Genome Anatomy Project (BTGAP), which NINDS initiated in cooperation with the National Cancer Institute, has found more than 1000 previously undiscovered human genes. In the past year by monitoring gene defects researchers have seen the first indications of success in predicting which brain tumors will respond best to which therapeutic approaches. In the long run understanding the genetic basis of brain tumors will help scientists develop therapeutics more precisely targeted to the what causes tumors.

Plasticity: Plasticity, that is, the capacity for the brain to adapt to experience, the environment, disease, and injury, is a major unifying theme in neuroscience that complements the findings from genetics. At the molecular and cellular level, for example, researchers this year discovered that manipulation of a single gene in rodents that codes for a protein called integrin stimulated nerve cells to grow in damaged spinal cords. At the behavioral level, findings this year present strong evidence for the importance of sleep in consolidating the effects of experience during development and clues to the broader mystery of why we need sleep. Researchers are also using brain imaging to determine why only some stroke victims recover lost language abilities and to develop strategies to augment adaptive plasticity using behavioral methods, noninvasive stimulation, and drugs. There is also a dark side to brain plasticity–maladaptive plasticity may contribute to a wide range of problems such as dystonia, epilepsy, and chronic pain states. Understanding brain plasticity, from molecules to behavior, has broad implications for confronting disease and maintaining a healthy brain throughout life.

Stem cells: For no area of medicine are stem cells more promising than for disorders of the nervous system. In animal studies, stem cells have shown benefits for disorders as diverse as Parkinson's, stroke, spinal cord injury, muscular dystrophy, and inherited metabolic diseases of children. Scientists are beginning to learn what signals tell stem cells to multiply and specialize. NINDS Intramural researchers, for example, have coaxed embryonic mouse stem cells to efficiently form dopamine nerve cells, the type lost in Parkinson's disease. With slight changes in instructions the same cells can form structures with the multiple cell types of normal pancreatic islets. When transplanted to rodents these pancreas-like cells survived and produced insulin in response to blood sugar, though not enough yet to cure diabetes. Other scientists have isolated neural stem cells from adult human brain tissue removed for therapeutic surgery, from adult human brains after death, and have found bone marrow can make nerve-like cells. Consistent with the President's August 9, 2001 stem cell research policy efforts are underway to compare stem cells from various sources and see which might be best suited for the many different therapeutic purposes. However, the well-justified enthusiasm of scientists for stem cells is tempered with caution, and extensive research is necessary before any approved stem cells may safely and effectively treat people.

Encouraging the brain's resident stem cells: One dramatic aspect of brain plasticity is the newly discovered capacity of even adult brain to make new nerve cells. Scientists are beginning to understand how behavior and the environment influence the formation of new cells. Scientists have shown that even a simple exercise like running can increase the production of brain cells in rodents. Investigators found that mice with the same genetic defect as children with ataxia-telangiectasia made new brain cells at higher rates than normal, but the rate did not respond as strongly to running, and most new cells were glial cells rather than nerve cells. Finding stimuli that affect cell proliferation within the brain may be a new therapeutic strategy for many diseases.

Common mechanisms of disease: Common themes are emerging as scientists unravel the cascades of processes that underlie various neurological diseases, leading to the hope that similar therapeutic strategies will also apply. Excessive release of the neurotransmitter glutamate, which electrically activates (excites) nerve cells, is implicated in "excitotoxity" that contributes to brain and spinal cord damage in stroke, trauma, multiple sclerosis, and neurodegenerative diseases. Recently scientists added another example to this list with evidence that brain tumors expand by killing surrounding nerve cells via a similar mechanism. Other findings this year reinforce the notion that abnormal calcium handling within nerve cells, highly reactive chemicals called free radicals, abnormal protein aggregation, and activation of "cell suicide" programs called apoptosis are common mechanisms in many different neurological disorders.

Pain: Pain is the most common reason people seek medical help, and scientists are identifying the mechanisms that underlie persistent pain conditions such as inflammatory pain. At the site of painful inflammation the enzyme COX-2 makes substances called prostaglandins which heighten the sensitivity of nerves to pain. Drugs that prevent COX-2 from making prostaglandins are widely used as pain medications. Last year scientists studying inflammatory pain in rats discovered that inflammation regulates the COX-2 enzyme within the spinal cord and brain as well as at the local site of inflammation. Developing drugs that interrupt the pain signals in the brain and spinal cord should lead to more effective control of pain and perhaps also for the fever, lethargy, and loss of appetite mediated by the brain that often accompany infection.

Higher brain functions: Brain imaging revolutionized studies of higher brain functions like thinking, memory, and emotions. Methods such as functional magnetic resonance imaging (fMRI) allow researchers to monitor which parts of the brain come into play as people carry out behavioral tasks. Other technologies complement brain imaging. This year scientists used transcranial magnetic stimulation (TMS) to activate or inhibit parts of the brain, and resolve long-standing questions about whether fMRI signals reflect activation or inhibition of nerve cells. In other TMS experiments scientists showed that part of the cerebral cortex called the left dorsolateral prefrontal cortex is critical for abstract reasoning, confirming what imaging studies had suggested. Because TMS can modulate brain plasticity, it is also under investigation as a therapy for several disorders. Another technology, microelectrode recording, identified in monkeys individual nerve cells in the prefrontal cortex that can encode abstract rules. Understanding higher brain functions, through a variety of methods, is critical for disorders as diverse as stroke, traumatic brain injury, neurodegenerative disorders, and autism.

DIAGNOSING, TREATING AND PREVENTING NERVOUS SYSTEM DISORDERS

Developing treatments and preventive measures for nervous system disorders requires a spectrum of research from experimental therapeutics in cells and animals through clinical trials in human patients. NINDS balances efforts against many different disorders, using therapeutic strategies that include drugs, surgery, diet, behavior, immune, gene and cell based therapeutics. The Institute must continue refining existing therapies while encouraging new approaches at the frontiers of medical science.

Diagnosis: Diagnosing neurological disorders is essential for physicians to devise the best treatment. Advances in genetics, brain imaging, and other technologies are helping physicians to determine which of the huge variety of nervous system disorders afflict a patient. As we learn to slow the course of neurodegenerative disease, early diagnosis will becomes all the more crucial. In Parkinson's disease, for example, more than two thirds of dopamine cells in the substantia nigra (part of the brain's motor control system) may have already died by the time the disease is detected. A few recent highlights illustrate progress in diagnosing neurological disorders:

Predicting stroke outcome: Scientists have developed a new analytical tool to predict early on how well a person will recover from a stroke. The procedure combines diffusion weighted magnetic resonance imaging of the brain (an adaptation of the standard MRI), the National Institutes of Health Stroke Scale (a widely used clinical measure of neurological dysfunction) and the time from the onset of symptoms to the brain scan. The combined scale predicts stroke recovery with high sensitivity and specificity, which should help physicians manage patients more efficiently and reduce distress and anxiety among patients and families.

Early detection of intractable epilepsy: A new study provides physicians with much needed guidance for predicting early which children with epilepsy will develop intractable forms of the disease. To gather a widely representative group of children researchers recruited from academic centers, private practices, and community clinics. The study found that clinical classification of epilepsy syndromes, high initial seizure frequency, and certain EEG (brain wave) findings could predict early in the course which children will develop intractable epilepsy. There are a wide variety of surgical and drug treatments for epilepsy, and this new information will be helpful in developing treatment strategies. More aggressive treatment carries risks, but might be appropriate for children whose epilepsy is likely to be intractable.

Identifying a treatable subtype of ataxia: The many inherited ataxias have long defied attempts at rational diagnosis and classification, but are yielding in recent years with the identification of more than a dozen different genes that, when defective, can cause these movement disorders. The cumulative results are leading to improvements in diagnosis and understanding of what causes these disorders. A new study examining patients with unexplained ataxia (loss of movement coordination) found cases associated with defects in coenzyme Q-10, which is a crucial component in cells' energy economy. Once identified, patients responded to dietary supplementation of coenzyme Q-10 with improved ataxia, increased strength, and less frequent seizures.

Experimental therapeutics: Studies in cells and animals develop new therapies and ensure that a treatment or preventive measure is likely to be safe and effective before testing in people can begin. NINDS has a long history in experimental therapeutics targeting diverse scientific and technical strategies, through a variety of support mechanisms, working with academic centers and private business enterprises. Since 1975, for example, the NINDS Epilepsy Therapeutic Research Program has worked with industry to test more than 20,000 compounds for their anti-convulsant properties, including some now in use as drugs. 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, and this program is also focusing its expertise on the development of chronic brain stimulation therapies which have the potential to treat several disorders. NINDS work in developing gene and stem cell therapies is also continuing. In the pharmacological arena the Institute has begun new programs to screen FDA approved compounds and to develop high throughput screening centers for neurodegenerative diseases. A few finding illustrate the broad area of experimental therapeutics:

Moving towards drugs for prion diseases: Creutzfeldt-Jakob disease (CJD) is a devastating neurodegenerative disorder with no known treatment. CJD is in the same class of unusual diseases that includes bovine spongiform encephalopathy (BSE). Rogue proteins called prions appear to cause these disorders by forming harmful aggregates in the brain, so researchers developed a cell culture screening test for compounds that might prevent or clear the abnormal prion aggregates. Two drugs which proved effective in these cell culture tests are already approved for other medical uses: chlopromazine, used for the treatment of schizophrenia, and quinacrine (or atabrine), widely used during World War II for malaria. Testing of these compounds in people with vCJD, the form of disease linked to BSE, is planned in the United Kingdom. In FY01 NINDS initiated a program to systematically test FDA approved drugs in cell based screens for possible use against other neurodegenerative diseases .

Antisense therapy: The logic of antisense therapy is quite compelling. The DNA of our genes directs the formation of RNA, which cells in turn read out to form proteins. Every DNA and RNA strand has an exact complement, like the two strands of the DNA double helix. So, introducing a molecule that is the exact match (antisense) for an RNA that codes for a harmful protein should lock up the RNA and prevent the production of that protein. In practice, however, success has been limited by the difficulty of delivering antisense molecules where needed. Now scientists have developed a chemically modified type of antisense molecule directed against amyloid beta protein, which forms clumps in the brains of people with Alzheimer's and contributes to the disease. When introduced intravenously, the antisense agent reversed learning and memory deficits in mice with an Alzheimer's-like disease. Much work is needed before such a treatment could safely be applied to people, but the potential of antisense therapy is tantalizing for the many diseases in which a mutant protein causes harm.

Protecting against brain trauma: Creatine is a common food supplement that is especially favored by athletes. Muscle naturally contains high concentrations of creatine which serve as an energy source during heavy exercise. In recent years, scientists, increasingly aware of how energy metabolism is implicated in neurological disorders, have found that creatine supplementation may partly reduce damage in animal models of stroke, muscular dystrophy and

Huntington's disease. In the most recent study, chronic administration of creatine reduced brain damage from experimental traumatic injury by more than one third in mice and about half in rats. This provides clues to the mechanisms responsible for damage following traumatic brain injury and may lead to use as a neuroprotective agent, especially in athletes who have an increased risk of blows to the head.

Clinical testing treatments and preventive measures: NINDS has pioneered clinical trials to test the safety and effectiveness of interventions to treat or prevent neurological disorders, including trials that showed the first effective acute treatments for stroke and for spinal cord injury. In recent years the Institute implemented new grant mechanisms for planning trials and for pilot trials, new procedures to ensure that trial design is optimal, increased professional staff to support clinical trials design and monitoring, and a subcommittee of the Council to oversee clinical trials activities.

Ongoing clinical trials, in both intramural and extramural divisions, focus on prevention and on treatment. Studies range from planning stages, through small phase I and II investigations, to large phase III multi-center projects. Trial interventions run the gamut, including drugs, surgery, gene therapy, chronic brain stimulation, hormone therapy, cell transplantation, hypothermia, transcranial magnetic stimulation, radiosurgery, immunotherapy, diet, behavioral, social, and rehabilitation methods. A partial list of disorders targeted in ongoing trials includes: AIDS, ALS, brain tumors, cerebral palsy, attention deficit hyperactivity disorder, brain trauma, Turner syndrome, Parkinson's disease, neurocysterosis, Lyme disease, migraine, sleep disorders, dystonia, Herpes zoster and postherpetic neuralgia, hereditary ataxias, multiple sclerosis, pain, spinal muscular atrophy, and stroke. A few recent results illustrate progress in this area:

Protecting the brains of infants during surgery for high-risk heart defects: Each year about 30,000 infants in the United States are born with congenital heart disease and at least a third need surgery during infancy. In hypoplastic left heart syndrome (HLHS) the heart is severely underdeveloped and unable to pump enough blood. HLHS was invariably fatal until surgeons developed methods to repair the defect in the 1980's. Since then survival rates have been improving, but neurological damage often occurs due to the stress of the surgery, which requires stopping the heart, cardio-pulmonary bypass, lowering the infant's body temperature, and then reversing the procedure, which itself has risks. A clinical trial has now demonstrated that the drug allopurinol helps reduce the risks of surgery in infants with HLHS. Allopurinol is widely used to treat gout in adults. The researchers chose the drug because it may scavenge or inhibit the formation of free radicals. These highly reactive chemicals are formed by the body during these circumstances and in several other acute and chronic neurological disorders, so the results may have wider implications.

Safe emergency treatment for seizures: A new study shows that paramedics can safely and effectively treat patients who are suffering from acute and prolonged seizures with injections of benzodiazepines, a mild form of tranquilizers. The study included patients diagnosed with "status epilepticus," continuous or repeated seizures lasting 5 minutes or more without recovery of consciousness. A patient who is in status epilepticus needs to be treated as quickly as possible in order to prevent serious neurological damage. This study demonstrates that there is a safe and

early treatment for a serious condition and helps pave the way for testing future emergency response interventions.

Nicotine patch helps control the symptoms of Tourettes syndrome in children: A clinical trial jointly funded by NINDS and the Tourette's Syndrome Association of America showed that a nicotine patch helps control the symptoms of Tourette's syndrome in children and adolescents. The use of the patch allowed physicians to control symptoms, including motor tics, with much lower doses of the drugs normally used to treat the disorder. These drugs often have strong unwanted effects on movement control and thinking, so reducing doses is important. There was no evidence of nicotine dependence in this study, but scientists are looking for other drugs that can mimic the effects of nicotine without its addictive risks and side effects.

Enzyme replacement therapy for Fabry disease: In hereditary "storage" disorders such as Fabry disease the body lacks a normal enzyme that breaks down and recycles certain body chemicals, so partially broken down substances accumulate to harmful levels. Fabry disease typically first becomes apparent during childhood or adolescence with recurrent episodes of severe pain in the hands and feet, skin lesions, and damage to the cornea, and usually progresses to cause death through effects on the kidneys, heart, or blood vessels of the brain. NINDS intramural researchers first demonstrated that intravenous administration of the missing enzyme (α-galactosidase A) temporarily reduced the levels of the harmful substance (globotriaosylceramide) in the blood of patients with Fabry disease. After developing adequate supplies of the enzyme using recombinant DNA technology (a difficult task in itself), researchers conducted a small phase I clinical trial which found that the enzyme could be administered safely. A randomized, controlled phase II clinical trial has now shown that the therapy 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.

Managing chronic tension-type headache: Tension headaches involve a prolonged and painful tightening of head and neck muscles. About 2-3% of Americans experience these headaches chronically, more than 15 days each month, nearly every day for some people. Overuse of over-the-counter analgesics can make the problem worse. There has been conflicting evidence about the effectiveness of tricyclic (referring to the chemical structure) drugs for chronic tension headache, and little information about the relative effectiveness of behavioral interventions alone and in combination with the drugs. A randomized, controlled clinical trial evaluated two tricyclic drugs alone or in combination with behavioral stress management. The results showed that the drugs and the behavioral therapy each improved headaches better than placebo. The drugs acted more quickly than the stress management program, but the patients who received the combination of drugs and behavioral treatment were, in the long run, most likely to show improvement. The active treatments reduced the number of days with at least moderately severe headache from about 14 days to fewer than 7 days a month.

Story of Discovery: Preventing Strokes

Stroke is the third leading cause of death in the United States, ranking below only heart disease and cancer. The estimated 4.4 million stroke survivors [*Stroke*, Jan. 2001 32:280-299] often suffer serious, long-term disability. Because the likelihood of stroke – or "brain attack"– increases with age, and the American population is aging, the number of strokes is increasing. However, without the remarkable progress in stroke prevention, which reflects sustained efforts of private organizations, NIH, and other government agencies, the toll of stroke would be dramatically worse. As NINDS celebrates its 50th anniversary, the U.S. Centers for Disease Control and Prevention estimates that the age-standardized stroke death rate declined by 70% for the U.S. population from 1950 to 1996 [*MMWR Weekly* 48:649-56 1999], and the American Heart Association tallies a 15% decline just from 1988 to 1998.

NINDS research led to the first acute treatment proven to improve the outcome from ischemic stroke, tissue plasminogen activator or t-PA, and efforts are underway to develop even better interventions to promote recovery. Yet, most of the reduced death rate to date comes from research on stroke prevention, and NINDS has contributed substantially to this growing body of knowledge. Over the past two decades, advances in stroke research have taught us that there is no "one size fits all" approach to preventing stroke. Millions of Americans live with a variety of risk factors – heart irregularities, hypertension, narrowed arteries, diabetes, and others. In addition, women and minorities, as well as people living in specific geographic regions, have unique stroke risks that must be addressed independently from other risk factors. Stroke prevention requires attention to a variety of strategies.

The large Stroke Prevention in Atrial Fibrillation (SPAF) studies of the 1980's and 1990's illustrate how medical management has contributed to stroke prevention. For many years, aspirin and warfarin – two anti-clotting drugs with different safety profiles and monitoring requirements – were used to prevent stroke in patients with atrial fibrillation, a common disorder of irregular heart rate and rhythm, and a significant stroke risk factor. However, use of these agents was based on little hard scientific evidence. The SPAF trials indicated that both aspirin and warfarin are effective and have a place in the prevention armamentarium, but that each drug has a better risk/benefit ratio for a different group of patients. Other studies, such as the Warfarin Antiplatelet Recurrent Stroke Study, the Vitamin Intervention for Stroke Prevention study, the African-American Antiplatelet Stroke Prevention Study, and the Women's Estrogen for Stroke Trial, build on these earlier findings, and continue to add to our knowledge about medical interventions that can affect the incidence of stroke in different at-risk groups.

The NINDS has also supported several major studies in the surgical prevention of stroke. This work has particular significance for people with carotid artery stenosis, a narrowing of the major blood vessels that supply the brain. One definitive study in the late 1970s examined a procedure called extracranial/intracranial (EC/IC) bypass. EC/IC bypass had been used for several years as a means to restore blood blow to the brain. The NINDS-funded study of the procedure's effectiveness found that the data did not support its continued use in medical practice. Although these findings were negative, they were of significant benefit to patients, who could avoid the risks of this surgery, and to researchers, who used this information to redirect their attention to

other promising approaches. As a result, investigators explored an alternative strategy to the bypass surgery, called carotid endarterectomy, which involves the removal of fatty deposits in the carotid arteries. This approach was shown to have substantial benefit, in both the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the North American Symptomatic Carotid Endarterectomy Trial (NASCET), for people who meet certain criteria. As with other prevention strategies, NINDS continues to evaluate surgical interventions, particularly as new techniques are developed.

Researchers are continuing to examine gaps in the field of stroke prevention that might benefit from controlled clinical study. Recently, researchers evaluated the risk of stroke after a transient ischemic attack (TIA), or "mini-stroke." The symptoms of TIAs pass quickly, usually within a day, and are often ignored. After following 1700 people with a TIA, the study found that these episodes warn of a dramatically increased likelihood of experiencing a stroke within a 90-day period–more than 50 times compared with other people of the same age. Other risk factors, such as advanced age, other health conditions, and severity of the TIA, also helped to predict stroke risk, and may be useful in determining whether patients should be hospitalized immediately and/or receive preventive interventions following a TIA. Heeding the warning of a TIA may help people avoid a catastrophic stroke.

The incremental nature of progress in stroke prevention has confirmed that there is no easy route to success. The broad portfolio of NINDS research on stroke offers a glimpse of what the future might bring—the possibility of vaccines, genetic tests to tailor preventive measures for each individual, studies that may link infections or inflammation within blood vessels to stroke, and new information about how chronic stress and hormones may affect susceptibility to stroke damage. The NINDS five-year plan for stroke research and the Institute's planning efforts targeting health disparities in stroke will guide these activities to produce continued advances in stroke prevention.

NINDS is also strongly committed to expanding its programs to educate clinicians and the public about important research findings. NINDS was a key participant in organizing The Brain Attack Coalition - a group of professional, voluntary and governmental entities dedicated to reducing stroke occurrence, disabilities and death - and the Coalition's website is maintained by NINDS staff. In addition, in May 2001, the NINDS launched a national public education campaign, *"Know Stroke: Know the Signs. Act in Time."* Each year, only a fraction of stroke patients arrive at the hospital in time to receive the only proven acute treatment that makes the difference between disability and full recovery in ischemic stroke, the "clot buster" t-PA. This campaign is designed to help people recognize the symptoms of stroke and appreciate their urgency, in order to obtain medical help in time.

The gains from stroke prevention research each year may be incremental in their effect on national statistics, but even a small drop in the stroke rate means a dramatic difference for many people and their families, and over time the advances in stroke prevention research are having a major impact on the nation's health.

INITIATIVES

The NIH system of unsolicited grant proposals and peer review is especially suited to confronting the extraordinary variety of disorders that affect the nervous system and the broad scope of science that is essential to progress. This process engages the collective wisdom and ingenuity of the scientific community to seek out the most pressing needs and the best opportunities. Unsolicited grants, however, are not always sufficient for NINDS to carry out its mission most effectively. The Institute takes more directed action when public health burdens dictate or emerging scientific opportunities require special resources or funding mechanisms. Formal planning efforts guide NINDS actions, including a strategic planning process, disease specific planning, and workshops focused on specific topics, all with the oversight of the Congressionally chartered NINDS Council.

The NINDS strategic planning process began in 1998 and drew upon the nations' leading scientists and physicians, the public, and Institute staff. The effort coalesced around cross-cutting themes of neuroscience and developed the *NINDS Strategic Plan: Neuroscience at the New Millenium* available at: http://www.ninds.nih.gov/about_ninds/strategic_plan.htm. Strategic planning sets the overall framework for the future. The *Parkinson's Disease Research Agenda* represents the first of a series of disease specific planning efforts that build on that foundation. Implementing disease specific plans, such as the Agenda, requires a multi-faceted effort involving several grant and contract support mechanisms, meetings large and small, and extensive professional staff involvement.

FY01-02 Workshops and Solicitiations: In FY01 NINDS, often working together with other components of NIH and private groups, held workshops focused on disorders including autism, dystonia, epilepsy, HIV and the nervous system, mental retardation and developmental disorders, multiple sclerosis, neuroborreliosis, pain, Parkinson's disease, stroke, spinal cord injury, and neurocognitive changes following cardiac surgery. Other workshops focused on cross-cutting topics such as brain banking, cognitive and emotional health in minority children, cognitive neuroscience and brain imaging, DNA damage in neurodegeneration, functional genomics in the nervous system, gene therapy, the healthy brain project, neural prostheses, and regeneration and synapse formation.

NINDS also issued program announcements, requests for grant applications, and requests for contracts in several topics, reflecting recommendations of planning groups, workshops, and the scientific community. Several of these, as enumerated above, reflect the continuing efforts to implement the Parkinson's Disease Research Agenda. Others topics included: exploratory/developmental epilepsy awards for junior investigators, pilot studies for clinical trials, clinical trials planning grants, specialized program of translational research in acute stroke, administrative supplements for research infrastructure for neuro-AIDS research projects, effects of hypoglycemia on neurons and glia cell function, gene therapy for neurological disorders, gene discovery for neurological and neurobehavioral disorders, microarray centers for research on the nervous system, research on research integrity, biology of non-human stem cell in the environment of the nervous system, functional microstimulation of the lumbrosacral spinal cord, gene expression profiling in the nervous system following traumatic spinal cord injury,

cognitive neuroimaging, restless legs syndrome and periodic limb movement disorder, and specialized neruoscience research programs in heath disparities. Solicitations also included those carried over from the previous year, such as exploratory grants in pediatric brain disorders and pathogenesis and therapy of the muscular dystrophies, and a variety of programs to support training in basic and clinical neuroscience.

NINDS also participated in solicitations developed by, or in cooperation with, other NIH components of NIH in many areas relevant to the Institute mission, such as autism research and autism centers, pediatric clinical trials, diabetes, cachexia, Alzheimer's disease, attention deficit hyperactivity disorder, stem cells, chronic pain, facioscapulohumeral muscular dystrophy, ethical issues, HIV/AIDS and several cross cutting aspects of genetic research and bioengineering.

New initiatives for FY03: In addition to continuing initiatives begun in previous years, such as implementation of the Parkinson's Agenda, the Institute will undertake new or expanded efforts in several areas during FY03. NINDS initiatives for FY03 arise from ongoing planning efforts, as well as those highlighted by Congress.

In March 2000 NINDS led a landmark conference "Curing Epilepsy: Focus on the Future." The conference began a process through which epilepsy researchers, private health advocates, and NINDS staff formulated "benchmarks" for epilepsy research [on the web at: http://www.ninds.nih.gov/about_ninds/epilepsybenchmarks.htm]. This planning effort is continuing to assess how NINDS can best achieve those goals and is developing specific initiatives.

In July 2000 NINDS and the National Cancer Institute together convened a *Brain Tumor Progress Review Group (PRG)* as the beginning of a systematic reappraisal and planning effort for brain tumor research. The PRG included more than 100 scientists, physicians, and representatives of voluntary groups, as well as NIH intramural scientists and professional staff. The subgroups presented more than a dozen detailed reports of various aspects of brain tumor biology and treatment available at: http://www.ninds.nih.gov/about_ninds/btprg/frontpage.htm. The PRG process is proceeding to assess ongoing activities against the identified needs and to recommend specific initiatives.

NINDS held the initial meetings of a *Stroke PRG* in July 2001. This meeting also involved more than 100 stroke researchers, physicians, representatives of voluntary groups, and NIH professional staff. The stroke PRG is following the same process as the Brain Tumor PRG. The initial reports are in the final stages of preparation and the planning process will continue to assess current activities against future needs and recommend specific NINDS actions in the following months.

In May 2000 NINDS issued a *Five Year Strategic Plan on Minority Health Disparities* [available on the web at: http://www.ninds.nih.gov/about_ninds/disparities.htm]. The Institute is proceeding with workshops in specific areas highlighted by the plan and an extensive program of research and training related to health disparities. The program of Specialized Neuroscience Research Programs (SNRPs) is an integral part of this and has been expanded as of FY01 to include 10 SNRPS.

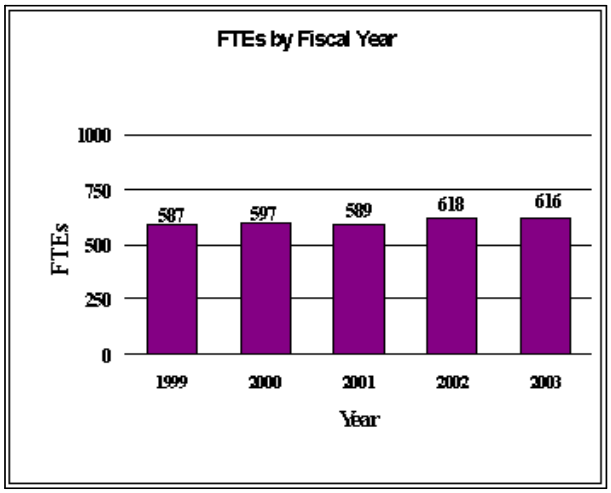
NINDS is coordinating the NIH role in the *DHHS Bovine Spongiform Encephalopathy/ Transmissible Spongiform Encephalopathy (BSE/CJD)Action Plan* continuing its history of research in this area. Landmark intramural studies established the transmissibility of these diseases and extramural investigations advanced the "prion" theory to explain these unusual disorders, recognized in the 1976 and 1997 Nobel Prizes. In FY01 NINDS established a major contract effort to develop tests to ensure the safety of blood products and other tissues. NINDS is expanding efforts to understand these diseases, develop diagnostics, and devise therapies.

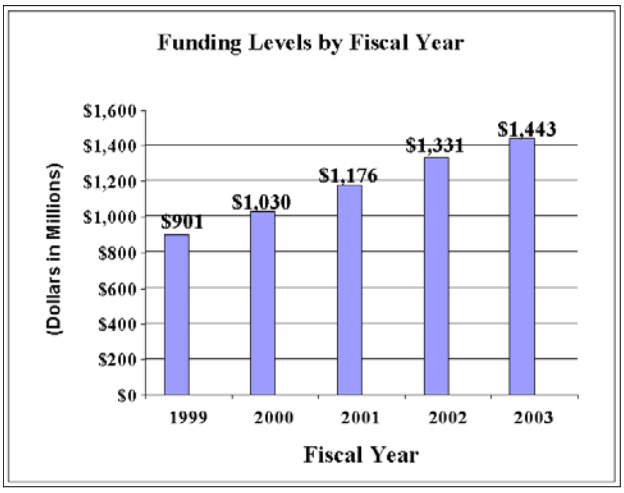
Finally, NINDS strategic panels, disease specific planning efforts and workshops all noted the importance of fostering increased efforts in translational research as the rapid progress in basic research presents increasing opportunities for fighting neurological disorders. Translational research bridges between the fundamental discoveries about the brain and disease and the specific information that is necessary to begin clinical trials of safety and efficacy. In FY03 the Institute will issue a comprehensive program designed to support translational research efforts. The program will 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.

BUDGET POLICY

The Fiscal Year 2003 budget request for the NINDS is $1,443,392,000 including AIDS, an increase of $111,744,000 and 8.4 percent over the FY 2002 level.

A five year history of FTEs and Funding Levels for NINDS are shown in the graphs below. Note that Fiscal Years 2000 and 1999 are not comparable for the Managerial Flexibility Act of 2001 legislative proposal.



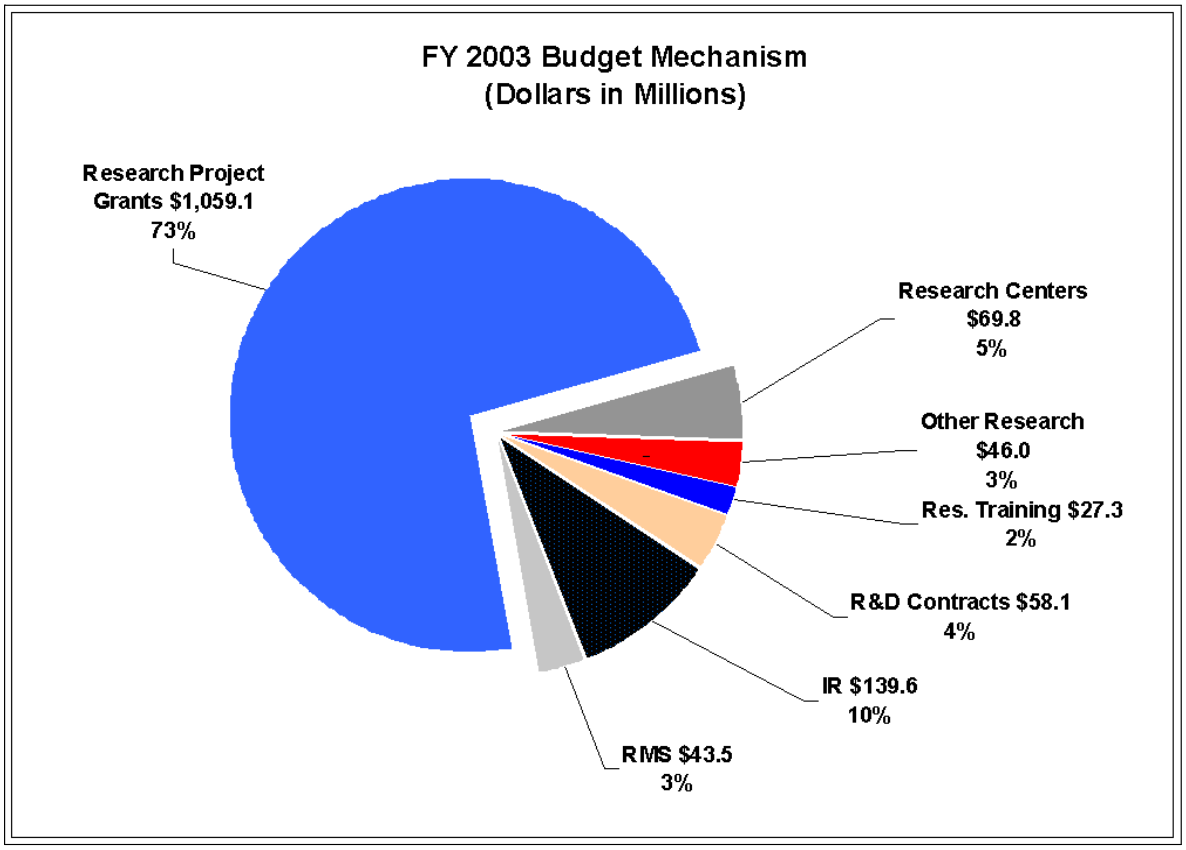


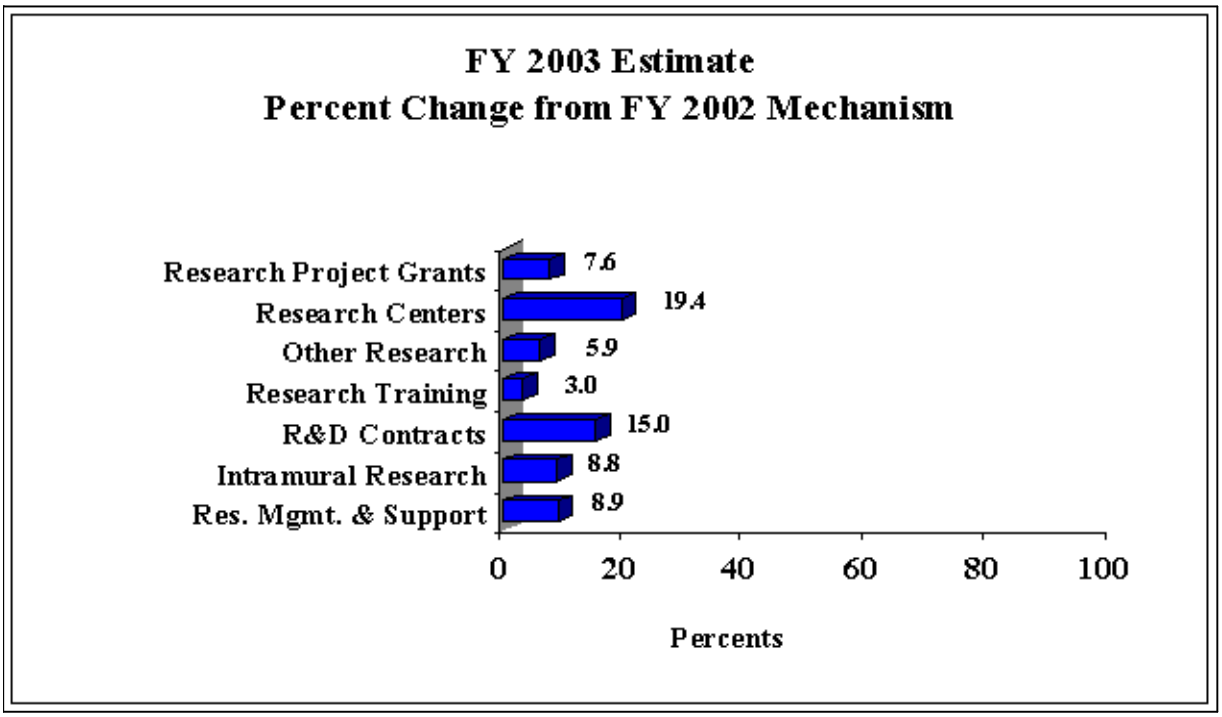
One of NIH's highest priorities is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The Fiscal Year 2003 request provides average cost increases for competing RPGs equal to the Biomedical Research and Development Price Index (BRDPI), estimated at 4.0 percent. Noncompeting RPGs will be funded at committed levels which include increases of 3 percent on average for recurring direct costs.

Future promises for advancement in medical research rest in part with new investigators with new ideas. In the Fiscal Year 2003 request, NINDS will support 612 pre- and postdoctoral trainees in full-time training positions, the same number as in FY 2002. Stipend levels for NRSA trainees will increase by 4 percent over Fiscal Year 2002 levels.

The Fiscal Year 2003 request includes funding for 58 research centers, 309 other research grants, including 214 clinical career awards, and 65 R&D contracts. The R&D contracts mechanism also includes support for 13 contracts for the Extramural Clinical and Pediatric Loan Repayment Programs. Intramural Research and Research Management and Support receive increases of 9 percent over FY 2002.

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





NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
TOTAL - Current Law
Budget Mechanism

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate		2003/2002 % Change	Avg. Cost % Change
Research Grants:	No.	Amount	No.	Amount	No.	Amount	No.	Amount		
Research Projects:										
Noncompeting	1821	$579,496,000	1999	$711,938,000	1999	$711,938,000	1983	$756,414,000	6.2	
Administrative supplements	(234)	$13,721,000	(260)	$12,000,000	(260)	$12,000,000	(260)	$12,000,000	0.0	
Competing:		0		0		0		0		
Renewal	236	$102,001,000	176	$78,228,000	176	$78,228,000	189	$87,469,000	11.8	
New	437	$150,719,000	438	$154,272,000	438	$154,272,000	471	$172,496,000	11.8	
Supplements	2	572,000	2	795,000	2	795,000	2	889,000	11.8	
Subtotal, competing	675	253,292,000	616	233,295,000	616	233,295,000	662	260,854,000	11.8	4.0
Subtotal, RPGs	2496	846,509,000	2615	957,233,000	2615	957,233,000	2645	1,029,268,000	7.5	
SBIR/STTR	88	23,022,000	111	27,342,000	111	27,342,000	121	29,876,000	9.3	
Subtotal, RPGs	2584	869,531,000	2726	984,575,000	2726	984,575,000	2766	1,059,144,000	7.6	
Research Centers:										
Specialized/comprehensive	47	56,232,000	49	58,500,000	49	58,500,000	58	69,840,000	19.4	
Clinical research	0	0	0	0	0	0	0	0	0.0	
Biotechnology	0	0	0	0	0	0	0	0	0.0	
Comparative medicine	0	0	0	0	0	0	0	0	0.0	
Research Centers in Minority Institution	0	0	0	0	0	0	0	0	0.0	
Subtotal, Centers	47	56,232,000	49	58,500,000	49	58,500,000	58	69,840,000	19.4	
Other Research:										
Research careers	180	23,043,000	201	25,066,000	201	25,066,000	214	26,695,000	6.5	
Cancer education	0	0	0	0	0	0	0	0	0.0	
Cooperative clinical research	2	2,786,000	45	7,300,000	45	7,300,000	45	7,300,000	0.0	
Biomedical research support	0	0	0	0	0	0	0	0	0.0	
Minority biomedical research support	5	1,454,000	7	1,900,000	7	1,900,000	9	2,565,000	35.0	
Other	34	7,778,000	40	9,150,000	40	9,150,000	41	9,425,000	3.0	
Subtotal, Other Research	221	35,061,000	293	43,416,000	293	43,416,000	309	45,985,000	5.9	
Total Research Grants	2852	960,824,000	3068	1,086,491,000	3068	1,086,491,000	3133	1,174,969,000		
Training:	FTTPs		FTTPs		FTTPs		FTTPs			
Individual awards	230	8,566,000	269	10,888,000	269	10,888,000	269	11,236,000	3.2	
Institutional awards	382	15,985,000	343	15,625,000	343	15,625,000	343	16,063,000	2.8	
Total, Training	612	24,551,000	612	26,513,000	612	26,513,000	612	27,299,000	3.0	
Research & development contracts	51	42,036,000	55	50,925,000	55	50,517,000	65	58,095,000	15.0	
(SBIR/STTR)	(12)	(3,687,000)	(10)	(2,800,000)	(10)	(2,800,000)	(10)	(2,800,000)		
	FTEs		FTEs		FTEs		FTEs			
Intramural research	408	110,643,000	421	125,580,000	421	125,580,000	419	136,882,000	9.0	
Research management and support	181	34,078,000	197	38,679,000	197	38,679,000	197	42,160,000	9.0	
Cancer prevention & control	0	0	0	0	0	0	0	0	0.0	
Construction		0		0		0		0	0.0	
Total, NINDS	589	1,172,132,000	618	1,328,188,000	618	1,327,780,000	616	1,439,405,000	8.4	
(Clinical Trials)		(73,518,000)		(83,562,000)		(83,562,000)		(91,137,000)		

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
TOTAL - Accrued Costs for Retirement and Health Benefits
Budget Mechanism

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate		2003/2002 % Change	Avg. Cost % Change
Research Grants:	No.	Amount	No.	Amount	No.	Amount	No.	Amount		
Research Projects:										
Noncompeting										
Administrative supplements										
Competing:										
Renewal										
New										
Supplements										
Subtotal, competing										
Subtotal, RPGs										
SBIR/STTR										
Subtotal, RPGs										
Research Centers:										
Specialized/comprehensive										
Clinical research										
Biotechnology										
Comparative medicine										
Research Centers in Minority Institutions										
Subtotal, Centers										
Other Research:										
Research careers										
Cancer education										
Cooperative clinical research										
Biomedical research support										
Minority biomedical research support										
Other										
Subtotal, Other Research										
Total Research Grants										
Training:	FTTPs		FTTPs		FTTPs		FTTPs			
Individual awards										
Institutional awards										
Total, Training										
Research & development contracts (SBIR/STTR)										
	FTEs		FTEs		FTEs		FTEs			
Intramural research	0	2,465,000	0	2,630,000	0	2,630,000	0	2,671,000	1.6	
Research management and support	0	1,107,000	0	1,238,000	0	1,238,000	0	1,316,000	6.3	
Cancer prevention & control	0	0	0	0	0	0	0	0	0.0	
Construction									0.0	
Total, NINDS	0	3,572,000	0	3,868,000	0	3,868,000	0	3,987,000	3.1	
(Clinical Trials)		(0)		(0)		(0)		(0)		

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
TOTAL - Proposed Law
Budget Mechanism

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate		2003/2002 % Change	Avg. Cost % Change
Research Grants:	No.	Amount	No.	Amount	No.	Amount	No.	Amount		
Research Projects:										
Noncompeting	1821	$579,496,000	1999	$711,938,000	1999	$711,938,000	1983	$756,414,000	6.2	
Administrative supplements	(234)	13,721,000	(260)	12,000,000	(260)	12,000,000	(260)	12,000,000	0.0	
Competing:										
Renewal	236	102,001,000	176	78,228,000	176	78,228,000	189	87,469,000	11.8	
New	437	150,719,000	438	154,272,000	438	154,272,000	471	172,496,000	11.8	
Supplements	2	572,000	2	795,000	2	795,000	2	889,000	11.8	
Subtotal, competing	675	253,292,000	616	233,295,000	616	233,295,000	662	260,854,000	11.8	4.0
Subtotal, RPGs	2496	846,509,000	2615	957,233,000	2615	957,233,000	2645	1,029,268,000	7.5	
SBIR/STTR	88	23,022,000	111	27,342,000	111	27,342,000	121	29,876,000	9.3	
Subtotal, RPGs	2584	869,531,000	2726	984,575,000	2726	984,575,000	2766	1,059,144,000	7.6	
Research Centers:										
Specialized/comprehensive	47	56,232,000	49	58,500,000	49	58,500,000	58	69,840,000	19.4	
Clinical research	0	0	0	0	0	0	0	0	0.0	
Biotechnology	0	0	0	0	0	0	0	0	0.0	
Comparative medicine	0	0	0	0	0	0	0	0	0.0	
Research Centers in Minority Institution	0	0	0	0	0	0	0	0	0.0	
Subtotal, Centers	47	56,232,000	49	58,500,000	49	58,500,000	58	69,840,000	19.4	
Other Research:										
Research careers	180	23,043,000	201	25,066,000	201	25,066,000	214	26,695,000	6.5	
Cancer education	0	0	0	0	0	0	0	0	0.0	
Cooperative clinical research	2	2,786,000	45	7,300,000	45	7,300,000	45	7,300,000	0.0	
Biomedical research support	0	0	0	0	0	0	0	0	0.0	
Minority biomedical research support	5	1,454,000	7	1,900,000	7	1,900,000	9	2,565,000	35.0	
Other	34	7,778,000	40	9,150,000	40	9,150,000	41	9,425,000	3.0	
Subtotal, Other Research	221	35,061,000	293	43,416,000	293	43,416,000	309	45,985,000	5.9	
Total Research Grants	2852	960,824,000	3068	1,086,491,000	3068	1,086,491,000	3133	1,174,969,000		
Training:	FTTPs		FTTPs		FTTPs		FTTPs			
Individual awards	230	8,566,000	269	10,888,000	269	10,888,000	269	11,236,000	3.2	
Institutional awards	382	15,985,000	343	15,625,000	343	15,625,000	343	16,063,000	2.8	
Total, Training	612	24,551,000	612	26,513,000	612	26,513,000	612	27,299,000	3.0	
Research & development contracts	51	42,036,000	55	50,925,000	55	50,517,000	65	58,095,000	15.0	
(SBIR/STTR)	(12)	(3,687,000)	(10)	(2,800,000)	(10)	(2,800,000)	(10)	(2,800,000)		
	FTEs		FTEs		FTEs		FTEs			
Intramural research	408	113,108,000	421	128,210,000	421	128,210,000	419	139,553,000	8.8	
Research management and support	181	35,185,000	197	39,917,000	197	39,917,000	197	43,476,000	8.9	
Cancer prevention & control	0	0	0	0	0	0	0	0	0.0	
Construction		0		0		0		0	0.0	
Total, NINDS	589	1,175,704,000	618	1,332,056,000	618	1,331,648,000	616	1,443,392,000	8.4	
(Clinical Trials)		(73,518,000)		(83,562,000)		(83,562,000)		(91,137,000)		

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
Budget Authority by Activity 1/
(dollars in thousands)

ACTIVITY	FY 2001 Actual		FY 2002 Estimate		FY 2003 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Extramural Research		$1,027,411		$1,163,521		$1,260,363		$96,842
		0		0		0		0
		0		0		0		0
		0		0		0		0
Subtotal, extramural research		1,027,411		1,163,521		1,260,363		96,842
Intramural research	408	113,108	421	128,210	419	139,553	(2)	11,343
Research managament and support	181	35,185	197	39,917	197	43,476	0	3,559
Total	589	1,175,704	618	1,331,648	616	1,443,392	(2)	111,744

1/ Please see the following tables for the crosswalk from current law to proposed law to reflect the administration's proposal for full accrued retirement and health benefits.

National Institutes of Health

National Institute of Neurological Disorders and Stroke

2001 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	2001 Actual Current Law	2001 Additional Accrual Costs	2001 Actual Proposed Law
Extramural Research:	$1,027,411	$0	1,027,411
Subtotal, extramural research	1,027,411	0	1,027,411
Intramural Research	110,643	2,465	113,108
Research management and support	34,078	1,107	35,185
Total	1,172,132	3,572	1,175,704

National Institutes of Health

National Institute of Neurological Disorders and Stroke

2002 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	2002 Current Estimate Current Law	2002 Additional Accrual Costs	2002 Appropriation Proposed Law
Extramural Research:	1,163,521	0	1,163,521
Subtotal, extramural research	1,163,521	0	1,163,521
Intramural Research	125,580	2,633	128,213
Research management and support	38,679	1,235	39,914
Total	1,327,780	3,868	1,331,648

National Institutes of Health

National Institute of Neurological Disorders and Stroke

2003 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	2003 Estimate Current Law	2003 Additional Accrual Costs	2003 Estimate Proposed Law
Extramural Research:	1,260,363	0	1,260,363
Subtotal, extramural research	1,260,363	0	1,260,363
Intramural Research	136,882	2,671	139,553
Research management and support	42,160	1,316	43,476
Total	1,439,405	3,987	1,443,392

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
Summary of Changes

2002 Estimated budget authority				$1,331,648,000
2003 Estimated budget authority				1,443,392,000
Net change				111,744,000
	2002 Current Estimate Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:	421		419	
a. Within grade increase		$40,211,000		$609,000
b. Annualization of January 2002 pay increase		40,211,000		483,000
c. January 2003 pay increase		40,211,000		784,000
d. Payment for centrally furnished services		28,092,000		2,528,000
e. Increased cost of laboratory supplies, materials, and other expenses		59,907,000		1,431,000
f. Accrued costs for retirement and health benefits		2,633,000		80,000
Subtotal				5,915,000
2. Research Management and Support:	197		197	
a. Within grade increase		17,715,000		295,000
b. Annualization of January 2002 pay increase		17,715,000		213,000
c. January 2003 pay increase		17,715,000		345,000
d. Payment for centrally furnished services		4,257,000		383,000
e. Increased cost of laboratory supplies, materials, and other expenses		17,945,000		474,000
f. Accrued costs for retirement and health benefits		1,235,000		39,000
Subtotal				1,749,000
Subtotal, Built-in				7,664,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
Summary of Changes--continued

CHANGES	2002 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	1999	723,938,000	(16)	44,476,000
b. Competing	616	233,295,000	46	27,559,000
c. SBIR/STTR	111	27,342,000	10	2,534,000
Total	2726	984,575,000	40	74,569,000
2. Centers	49	58,500,000	9	11,340,000
3. Other research	293	43,416,000	16	2,569,000
4. Research training	612	26,513,000	0	786,000
5. Research and development contracts	55	50,517,000	10	7,578,000
Subtotal, extramural				96,842,000
	FTEs		FTEs	
6. Intramural research	421	128,210,000	(2)	5,428,000
7. Research management and support	197	39,917,000	0	1,810,000
8. Construction		0	0	0
Subtotal, program		1,331,648,000		104,080,000
Total changes	618		(2)	111,744,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
Budget Authority by Object

	FY 2002 Appropriation	FY 2002 Current Estimate	FY 2003 Estimate	Increase or Decrease	Percent Change
Total compensable workyears:					
Full-time employment	618	618	616	(2)	-0.3
Full-time equivalent of overtime and holiday hours	2	2	2	0	0.0
Average ES salary	$139,783	$139,783	$144,186	$4,403	3.1
Average GM/GS grade	10.4	10.4	10.5	0.1	1.0
Average GM/GS salary	$66,733	$66,733	$69,936	$3,203	4.8
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$80,012	$80,012	$82,532	$2,520	3.1
Average salary of ungraded positions	$76,107	$76,107	$78,504	$2,397	3.1

	OBJECT CLASSES	FY 2002 Appropriation	FY 2002 Estimate	FY 2003 Estimate	Increase or Decrease	Percent Change
	Personnel Compensation:					
11.1	Full-Time Permanent	$27,253,000	$27,253,000	$28,462,000	$1,209,000	4.4
11.3	Other than Full-Time Permanent	13,016,000	13,016,000	13,596,000	580,000	4.5
11.5	Other Personnel Compensation	1,180,000	1,180,000	1,232,000	52,000	4.4
11.8	Special Personnel Services Payments	3,888,000	3,888,000	4,060,000	172,000	4.4
11.9	**Total Personnel Compensation**	**45,337,000**	**45,337,000**	**47,350,000**	**2,013,000**	**4.4**
12.0	Personnel Benefits	9,956,000	9,956,000	10,399,000	443,000	4.4
12.1	Personnel Benefits, Accrued Retirement Costs	2,633,000	2,633,000	2,715,000	82,000	3.1
13.0	Benefits for Former Personnel	0	0	0	0	0.0
	Subtotal, Pay Cost, Current Law	**55,293,000**	**55,293,000**	**57,749,000**	2,456,000	4.4
	Subtotal, Pay Cost, Proposed Law	**57,926,000**	**57,926,000**	**60,464,000**	**2,538,000**	**4.4**
21.0	Travel and Transportation of Persons	2,465,000	2,465,000	2,717,000	252,000	10.2
22.0	Transportation of Things	270,000	270,000	298,000	28,000	10.4
23.1	Rental Payments to GSA	0	0	0	0	0.0
23.2	Rental Payments to Others	1,560,000	1,560,000	1,725,000	165,000	10.6
23.3	Communications, Utilities and Miscellaneous Charges	1,080,000	1,080,000	1,189,000	109,000	10.1
24.0	Printing and Reproduction	840,000	840,000	938,000	98,000	11.7
25.1	Consulting Services	3,750,000	3,750,000	4,011,000	261,000	7.0
25.2	Other Services	14,607,000	14,607,000	16,103,000	1,496,000	10.2
25.3	Purchase of Goods and Services from Government Accounts	81,562,000	81,154,000	91,783,000	10,629,000	13.1
25.3	Accrued Retirement Costs	1,235,000	1,235,000	1,272,000	37,000	3.0
25.4	Operation and Maintenance of Facilities	6,080,000	6,080,000	6,696,000	616,000	10.1
25.5	Research and Development Contracts	23,924,000	23,924,000	27,752,000	3,828,000	16.0
25.6	Medical Care	160,000	160,000	179,000	19,000	11.9
25.7	Operation and Maintenance of Equipment	4,295,000	4,295,000	4,748,000	453,000	10.5
25.8	Subsistence and Support of Persons	0	0	0	0	0.0
25.0	**Subtotal, Other Contractual Services, Current Law**	**134,378,000**	**133,970,000**	**151,272,000**	**17,302,000**	**12.9**
25.0	**Subtotal, Other Contractual Services, Proposed Law**	**135,613,000**	**135,205,000**	**152,544,000**	**17,339,000**	12.8
26.0	Supplies and Materials	9,160,000	9,160,000	10,086,000	926,000	10.1
31.0	Equipment	10,135,000	10,135,000	11,160,000	1,025,000	10.1
32.0	Land and Structures	0	0	0	0	0.0
33.0	Investments and Loans	0	0	0	0	0.0
41.0	Grants, Subsidies and Contributions	1,113,004,000	1,113,004,000	1,202,268,000	89,264,000	8.0
42.0	Insurance Claims and Indemnities	0	0	0	0	0.0
43.0	Interest and Dividends	3,000	3,000	3,000	0	0.0
44.0	Refunds	0	0	0	0	0.0
	Subtotal, Non-Pay Costs, Current Law	**1,272,895,000**	**1,272,487,000**	**1,381,656,000**	**109,169,000**	**8.6**
	Subtotal, Non-Pay Costs, Proposed Law	**1,265,175,000**	**1,264,767,000**	**1,372,947,000**	**108,180,000**	**8.6**
	Total Budget Authority by Object, Current	**1,328,188,000**	**1,327,780,000**	**1,439,405,000**	**111,625,000**	**8.4**
	Total Budget Authority by Object, Proposed	**1,323,101,000**	**1,322,693,000**	**1,433,411,000**	**110,718,000**	**8.4**
	Total Accrued Retirement Costs	**3,868,000**	**3,868,000**	**3,987,000**	**119,000**	**3.1**

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
Salaries and Expenses

OBJECT CLASSES	FY 2002 Appropriation	FY 2002 Current Estimate	FY 2003 Estimate	Increase or Decrease
Personnel Compensation:				
Full-Time Permanent (11.1)	$27,253,000	$27,253,000	$28,462,000	$1,209,000
Other Than Full-Time Permanent (11.3)	13,016,000	13,016,000	13,596,000	580,000
Other Personnel Compensation (11.5)	1,180,000	1,180,000	1,232,000	52,000
Special Personnel Services Payments (11.8)	3,888,000	3,888,000	4,060,000	172,000
Total Personnel Compensation (11.9)	**45,337,000**	**45,337,000**	**47,350,000**	**2,013,000**
Civilian Personnel Benefits (12.1)	9,956,000	9,956,000	10,399,000	443,000
Accrued Costs of Retirement Benefits (12.1)	2,633,000	2,633,000	2,715,000	82,000
Benefits to Former Personnel (13.0)	0	0	0	0
Subtotal, Pay Costs, Current Law	**55,293,000**	**55,293,000**	**57,749,000**	**2,456,000**
Subtotal, Pay Costs, Proposed Law	**57,926,000**	**57,926,000**	**60,464,000**	**2,538,000**
Travel (21.0)	2,465,000	2,465,000	2,717,000	252,000
Transportation of Things (22.0)	270,000	270,000	298,000	28,000
Rental Payments to Others (23.2)	1,560,000	1,560,000	1,725,000	165,000
Communications, Utilities and Miscellaneous Charges (23.3)	1,080,000	1,080,000	1,189,000	109,000
Printing and Reproduction (24.0)	840,000	840,000	938,000	98,000
Other Contractual Services:				
Advisory and Assistance Services (25.1)	1,250,000	1,250,000	1,375,000	125,000
Other Services (25.2)	14,607,000	14,607,000	16,103,000	1,496,000
Purchases from Govt. Accounts (25.3)	28,807,000	28,807,000	32,939,000	4,132,000
Accrued Retirement Costs (25.3)	1,235,000	1,235,000	1,272,000	37,000
Operation & Maintenance of Facilities (25.4)	6,080,000	6,080,000	6,696,000	616,000
Operation & Maintenance of Equipment (25.7)	4,295,000	4,295,000	4,748,000	453,000
Subsistence & Support of Persons (25.8)	0	0	0	0
Subtotal, Other Contractual Services, Current Law	**55,039,000**	**55,039,000**	**61,861,000**	**6,822,000**
Subtotal, Other Contractual Services, Proposed Law	**56,274,000**	**56,274,000**	**63,133,000**	**6,859,000**
Supplies and Materials (26.0)	9,155,000	9,155,000	10,080,000	925,000
Subtotal, Non-Pay Costs, Current Law	**64,194,000**	**64,194,000**	**78,156,000**	**13,962,000**
Subtotal, Non-Pay Costs, Proposed Law	**65,429,000**	**65,429,000**	**79,428,000**	**13,999,000**
Total, Administrative Costs, Current Law	**119,487,000**	**119,487,000**	**135,905,000**	**16,418,000**
Total, Accrued Costs	**3,868,000**	**3,868,000**	**3,987,000**	**119,000**
Total, Administrative Costs, Proposed Law	**123,355,000**	**123,355,000**	**139,892,000**	**16,537,000**

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 2002 House Appropriations Committee Report Language

Item
Alzheimer's Disease -- NINDS continues to play an integral part in advancing science's understanding of Alzheimer's disease. Working collaboratively with the NIA, NINDS-supported researchers found that cortical degeneration or brain atrophy was 20 to 25 percent greater in patients with Alzheimer's. The Committee encourages NINDS to make Alzheimer's research a high priority and to continue to work closely with NIA and other Institutes. (p. 71)

Action taken or to be taken:
Alzheimer's disease 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 National Institute on Aging and other institutes that fund AD research. For example, NINDS is a member of 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 Alzheimer's disease. In a recent collaborative effort, NINDS joined NIA in organizing and sponsoring a meeting entitled "Synuclein and Cortical Lewy Bodies Associated with Dementia in AD, LBD, and PD." This meeting brought together investigators from several different areas of neurodegeneration research, who actively participated in an exchange of recent results and new ideas. Based on the success of this meeting, NINDS and NIA are acting as advisors on a cooperative agreement being submitted by one of the participating scientists to support a second meeting of this type in FY2003. NINDS also joined NIA in a solicitation for grant applications in the area of vaccines and immune therapy for Alzheimer's, released in December 2000. NINDS is currently co-sponsoring several grants with NIA that resulted from this request for applications, and the two Institutes continue to jointly monitor those awards.

Dystonia – The Committee continues to be interested in the extramural research portfolio of NINDS with respect to dystonia and encourages NINDS to continue to expand the study of the DYT1 gene and any other promising genetic leads. The Committee also encourages NINDS to enhance its collaboration with the dystonia research community in supporting epidemiological studies on dystonia and enhancing public an professional awareness of this disorder. The Director of the Institute should be prepared to provide a status report on the dystonia research portfolio at the fiscal year 2003 appropriations hearing.

Action taken or to be taken
NINDS has a substantial and increasing extramural program of dystonia research, which complements the continuing intramural efforts in this area. Intramural research aims to understand the brain dysfunctions that cause focal and generalized dystonias and to explore new

treatments, including drugs, motor training, and transcranial brain stimulation. The extramural program has increased professional staffing and undertaken activities to help stimulate research on dystonia. In January 2001 NINDS sponsored a workshop focused on genetic advances in dystonia. The Institute is also funding a major three-day symposium on the current status, recent advances, and potential new targets for research on all forms of dystonia. (The meeting was originally scheduled for September 2001 and has be re-scheduled for June 2002.) NINDS staff have met with leaders in dystonia research and dystonia foundation representatives to discuss future strategies and areas of cooperation. The Institute is funding a growing and diverse portfolio of extramural projects in dystonia research, including efforts to follow up on the DYT1 gene findings and to discover other genes that may contribute to dystonia. In addition to research focused directly on dystonia, NINDS supports extensive research on related movement disorders and basic and clinical research in areas that are likely to have an impact on understanding and treating dystonia in the future. These include studies of dopamine biology, brain plasticity, and how the brain controls movement, as well as efforts to develop treatment strategies such as brain stimulation and gene therapy.

Epilepsy --The Committee is encouraged by the development of 13 benchmarks for epilepsy research resulting from the Institute sponsored conference held in March 2000 on "Curing Epilepsy: Focus on the Future." The Committee urges NINDS to enhance research efforts in the prevention, treatment and eventual cure of this disease through all available mechanisms, as appropriate, including the development of a plan to implement the research benchmarks and establishment of an Interagency Epilepsy Coordinating Committee. The Committee also urges the Institute to enhance efforts to address research issues related to the impact of seizures on young children, women, the elderly and those with intractable or uncontrolled epilepsy. NINDS is also encouraged to develop research plans and goals for the anti-epileptic drug development program. The Director should be prepared to testify on its efforts to advance these areas of research at the fiscal year 2003 appropriations hearing. (p. 71)

Action taken or to be taken

NINDS is committed to both understanding the causes of and developing effective therapies for all forms of epilepsy. The March 2000 White House - initiated Conference "Curing Epilepsy: Focus on the Future," 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, galvanized the epilepsy research community to begin focusing on actually curing epilepsy (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. A major outcome of the meeting was the development of 13 research benchmarks that 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 already begun to implement several of these benchmarks, including holding workshops on "Models of Epileptogenesis and Epilepsy" and "Antiepileptic Drug Monotherapy Indications" (both held in March 2001) and planning a workshop on "Molecular Analysis of Complex Genetic Epilepsies," held January 31 - February 1, 2002. In addition, NINDS is actively working with epilepsy researchers and advocates to develop an overall plan to implement the benchmarks, beginning with a planning meeting which was held in December 2001.

Although NINDS is the lead NIH Institute for epilepsy research, several other NIH Institutes also fund epilepsy related projects, including National Institute of Mental Health, National Institute on Aging, , National Institute of Child Health and Human Development, and National Human Genome Research Institute. NINDS will work with these Institutes to coordinate epilepsy research efforts, including their involvement, as appropriate, in the implementation of the research benchmarks. This could include joint sponsorship of workshops and conferences, joint funding of initiatives, and periodic meetings to identify and discuss areas of common interest and opportunities for collaboration.

NINDS currently supports a number 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 several projects investigating the mechanisms of seizure onset in the developing brain, and the effects of seizures on children's cognitive, emotional and behavioral development. 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 is supporting epidemiology studies of the rates of epilepsy in the elderly, and 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, 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 trial portfolio is growing and encompasses a wide range of approaches to treating the disorder. In addition to the trials mentioned above, these includes two surgical protocols, one involving the use of radiosurgery ("gama knife") in treating mesial temporal sclerosis and, the other, electrical stimulation of the anterior nucleus of the thalamus as a novel treatment. Other trials include an investigation of the efficacy of the ketogenic diet, a pilot study of neurosysticercosis treatment, and treatment of depression. Over the past 25 years, the Anticonvulsant Screening Project (ASP), a component of the former program known as the Antiepileptic Drug Development Program, has, as part of NINDS's translational research effort, screened over 22,000 compounds for specific anti-epileptic and central nervous system effects. As a result, approximately 20 drugs have been evaluated in clinical trials, with five ultimately being made available for widespread clinical use in treating epilepsy. Several others are currently under clinical investigation. Currently, the Program is in the process of recruiting for a position to continue the emphasis on the search for new anti-epileptic agents while expanding screening activities for other neurological diseases. Future efforts are being directed towards the search for new models to treat highly resistant seizures, and to continue the search for treatment interventions that may prevent or cure disease.

Facioscapulohumeral Muscular Dystrophy - Facioscapulo-humeral muscular dystrophy (FSHD) is the third most common form of muscular dystrophy. The Committee is pleased that NINDS and NIAMS have taken steps to begin implementation of the recommendations of the 2000 research planning conference on FSHD and urges NINDS and NIAMS to develop a comprehensive research portfolio through all available mechanisms, as appropriate. (p. 72)

Action taken or to be taken
NINDS and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) are working together to implement the recommendations of the May 2000 FSH workshop, which the two Institutes organized in cooperation with the NIH Office of Rare Diseases, the FSH Society, and the Muscular Dystrophy Association of America. In September of 2000, the NIAMS and the NINDS funded a research registry for FSHD and myotonic dystrophy. The long-term goal of the registry is to facilitate research in FSHD and myotonic dystrophy by serving as a liaison between families affected by these diseases who are eager to participate in specific research projects, and investigators interested in studying these disorders. In November of 2000, the NIAMS and the NINDS jointly issued a request for applications for exploratory research on FSHD (R21 mechanism; RFA: AR-01-002). In January 2001 NINDS and NIAMS issued a PA-S (program announcement with set-aside) entitled "Therapeutic and pathogenic approaches for the muscular dystrophies" to encourage research in areas highlighted as priorities for MD research. The Institutes will continue to work together, and with other components of NIH as appropriate, to foster FSH research in the future.

Fragile X Syndrome–...The Committee urges 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 NINDS to coordinate these efforts with other Institutes working on related activities, including NIMH and NICHD. (p.72)

Action taken or to be taken
Fragile X Syndrome, a common cause of mental retardation, is one of several brain diseases linked to a type of genetic defect called a trinucleotide repeat expansion mutation. These kinds of mutations also cause Huntington's Disease, myotonic dystrophy, Friedrich's ataxia, spinocerebellar ataxia types 1, 2, 3, 6, and 7, spinobulbar muscular atrophy, and dentato-rubral pallido-luysian atrophy. Highlights of NINDS support for research in this area include a 2001 Gordon Research Conference on CAG triplet repeat disorders, focused on understanding the mechanisms by which triplet repeat expansions cause neurological disorders and encouraging young scientists to pursue research in this field.

NINDS has also partnered with the National Institute of Mental Health (NIMH) to launch a request for applications (RFA) to develop autism research centers of excellence (the STAART program) which proposes to include Fragile X patients as a comparison group. The Institute looks forward to continuing its interactions with NIMH and National Institute of Child Health and Development to develop a shared research portfolio on Fragile X syndrome and other triplet repeat diseases.

Mucolipidosis Type IV - The Committee commends NINDS for sponsoring research with the Mucolipidosis Type IV (ML4) Foundation. This research identified the gene whose mutation causes this debilitating genetic metabolic disease. The Committee urges NINDS and other Institutes to expand both intramural and extramural research on this disease. (p. 72)

Action taken or to be taken
NINDS continues its longstanding intramural and extramural commitment to research on Mucolipidosis Type IV (ML4) and other lysosomal storage disorders (LSDs). Intramural

researchers at NINDS continue their exploration of the genetics of this disease, by using cell culture preparations to study the location and function of the protein that causes ML4. NINDS-supported extramural researchers are also contributing to the efforts to unravel the molecular basis of this disorder. An impressive amount of knowledge has been gained about this disorder in recent years, including the finding that the mutant protein causing ML4 has features that may alter the electrical properties of affected cells. In September 2001, the Institute supported a meeting which brought researchers in ML4 together with scientists knowledgeable about how the mutant protein in ML4 can affect cellular activity. This workshop allowed a productive exchange between these groups, which should lead to a greater understanding of how gene and protein malfunctions in ML4 lead to the abnormal buildup of cellular material, and neurological degeneration. In addition to these activities, the Institute is also taking steps to overcome the common obstacles to gene therapy for many neurological diseases. In October 2000, NINDS co-sponsored a workshop on gene therapy, which focused in large part on LSDs. In July 2001, NINDS responded to interest at this workshop by co-sponsoring a Request for Applications on gene therapy approaches to many diseases, including ML4 and other genetic disorders.

Neurofibromatosis-The Committee encourages NINDS to expand its NF basic and clinical research portfolio through all available mechanisms, as appropriate, including clinical trials. The Committee commends NINDS for its leadership in initiating an NF workshop that involved other relevant NIH Institutes as well as the Army and VA. NINDS is encouraged to translate the recommendations of the workshop into research initiatives and to continue to coordinate its efforts with other Institutes engaged in NF research." (p. 72)

Action taken or to be taken

In May 2000, the NINDS held a two-day workshop to assess the status of NF research and to identify future research opportunities that could be developed in FY 2001. The NINDS has been vigorously engaged in the initiation of a broad spectrum of activities to respond to the needs and pursue the opportunities that were identified in that meeting.

In March 2001, NINDS issued a Request for Applications (RFA), in conjunction with the National Institute on Aging, and the National Institute of Mental Health,NIA, to promote research on the identification of genes that cause or contribute to human neurological and neurobehavioral diseases. The participating Institutes intend to commit a total of approximately $4 million in FY2002 to fund new grants submitted in response to this RFA; of this amount, NINDS will commit up to $3 million. This RFA was developed by NINDS as a direct result of the May 2000 workshop, as well as the comments provided by leading NF researchers on the type of directed research solicitations that likely would prove most useful in advancing NF research. The RFA (NS-02-002) specifically cites NF as a disease within the scope of its objectives. This solicitation was designed to encourage applications for genetics research projects to identify the gene or genes that produce disease susceptibility; to identify "modifier" genes that affect disease susceptibility or outcome; and to investigate the relationship between genotype and disease phenotype. These goals are particularly important with respect to NF research. Although the primary genes that cause NF1 and NF2 have been identified - neurofibromin and Merlin/schwannomin respectively - the modifier genes that contribute to determining the disease phenotype, that is, the clinical manifestations in individual patients, are

unknown. In addition, determining the relationship between specific NF1 and NF2 gene mutations carried by patients and their clinical manifestations, known as genotype-phenotype analysis, is of critical importance for the diagnosis and treatment of NF.

A critical bottleneck for NF research has been translating advances in basic research into diagnostic tools and clinical therapies. To accelerate this process, NINDS has developed a broad, overarching concept and series of mechanisms to facilitate translational research. The needs of the NF research and patient communities, as expressed in the May 2000 workshop and subsequent related discussions, served as both the impetus and a coalescing model for its development. NINDS expects to finalize and issue this translational research package by early 2002.

NINDS continues its longstanding outreach and support to the NF research and advocacy communities. Through a competitively awarded grant, NINDS was the major supporter of the National Neurofibromatosis Foundation (NNFF) sponsored meeting of the International Consortium for the Molecular Biology of NF1 and NF2 held May 20-23, 2001 in Aspen, Colorado. At this gathering of the world's leading scientists working on NF, new and exciting results were reported by a number of different investigators in studies ranging from animal models to tumors to learning disabilities. The meeting was also structured to attract exceptional new investigators to the field of NF research. NINDS also funded and moderated an NF "satellite" conference as part of a Child Neurology Society meeting in early November 2001 in Vancouver, British Columbia, which was extremely well-attended and well-received. Finally, NINDS is actively engaged in an advisory capacity in exploring the development, by the NF research community in conjunction with patient advocates, of a strategic plan for NF research, particularly in the area of clinical trials.

Spina Bifida–...The Committee urges NINDS to work with NICHD, AHRQ, and CDC to enhance efforts to assess and evaluate secondary prevention strategies to reduce the complications associated with spina bifida, including an evaluation of *in utero* surgical techniques through all available mechanisms, as appropriate, including a consensus conference. The Committee requests that the Director of the Institute be prepared to provide a progress report at the FY 2003 appropriations hearings. (p. 73)

Action taken or to be taken

NINDS supports a broad program of research on neurodevelopment and neurodevelopmental disorders, including spina bifida. Spina bifida results from a failure to close the developing neural tube, the embryonic structure that forms the brain and spinal cord. Both genetic and environmental factors appear to affect the incidence of neural tube defects. NINDS supported a recent conference for investigators from a variety of fields, including human genetics, embryology, dysmorphology, epidemiology, animal modeling, nutrition and molecular biology to share research findings on the underlying causes of neural tube defects and to promote interdisciplinary collaborations.

An increasing number of *in utero* surgical procedures are being performed as an intervention to reduce the complications associated with spina bifida despite the fact that *in utero* surgery has not been validated to show improvement over postnatal repair. In order to address this urgent

research need, the National Institute of Child Health and Human Development issued a notice of limited competition for spina bifida fetal surgery centers as an addition to its existing Maternal and Fetal Medicine Unit Network in March 2001. NINDS and NICHD have collaborated on other studies using the resources of this network, and NINDS has indicated its willingness to cooperate with NICHD, as necessary and appropriate, in providing advice and assistance to this program, particularly with regard to the evaluation of neurological outcomes.

Stroke–Stroke remains the third leading cause of death, a leading cause of permanent disability, and a major contributor of late-life dementia. The Committee encourages NINDS to place a high priority on stroke research. The Committee also encourages the Institute to expand its stroke education program and to initiate and continue innovative approaches to improve stroke diagnosis, treatment, rehabilitation and prevention through all available mechanisms, as appropriate. The committee looks forward to receiving the NINDS five-year strategic stroke research plan scheduled to be released this fall.

The committee encourages NINDS to support research and development in the area of polynitroxylated albumin as a neuroprotectant for ischemic, hemorrhagic and transient ischemic stroke through all available mechanisms, as appropriate. (p. 73)

Action taken or to be taken:

As part of the stroke strategic planning process, in July, 2001, the NINDS held a meeting of 150 nationally and internationally recognized stroke experts to identify gaps in stroke knowledge, and set research priorities. The attendees were divided into panels in fifteen topic areas. The report from this meeting will serve as a plan to improve stroke prevention, diagnosis, treatment and rehabilitation, building on current knowledge and identifying new approaches.

The clot-buster tPA is currently the only approved treatment for acute stroke. However, tPA has limitations and cannot be used in all situations; therefore, additional clotbusting and neuroprotectant agents must be developed. The NINDS is eager to support peer-reviewed applications for research and development of new potential stroke therapies, such as polynitroxylated albumin.

Tuberous Sclerosis **-** Tuberous sclerosis (TS) is a genetic disorder that affects many different organ systems. TS occurs in all races, both sexes, affects over one million individuals worlwide, and is the leading genetic cause of epilepsy and the second most identifiable cause of autism. The Committee encourages NINDS to enhance research in this area through all available mechanisms, as appropriate, including working collaboratively with private patient foundations to develop a research plan. (P. 73)

Action taken or to be taken:

Tuberous sclerosis, often referred to as tuberous sclerosis complex (TSC) is a genetic, neurological disorder primarily characterized by seizures, mental retardation, and skin and eye lesions. There can be great variability in the severity of symptoms. Benign tumors may grow on the face and eyes, as well as in the brain, kidneys, and other organs. Neurobehavioral problems and learning disabilities may also occur, and autism affects a significant percentage of TSC

patients. Epilepsy may be the most prominent feature, and seizures usually begin in the first year of life.

The NINDS has been working collaboratively and intently with patient advocacy organizations as well as the research community to stimulate tuberous sclerosis research, and to expand the base of investigators. As noted, epilepsy is a prominent condition in tuberous sclerosis, and the NINDS initiated contact with TS advocates in an attempt to include their interests and concerns at the recent meeting to develop benchmarks for epilepsy research. NINDS will make every effort to stimulate the development of a research plan for tuberous sclerosis, and consider all available mechanisms for encouraging research.

SENATE

Alzheimer's disease - NINDS continues to play an integral role in advancing science's understanding of Alzheimer's, a progressive brain disorder that results in memory loss, behavior and personality changes, and a decline in thinking abilities. Working collaboratively with NIA, NINDS-supported researchers found that cortical degeneration, or brain atrophy, was 20 to 25 percent greater in patients with Alzheimer's, confirming this as the major basis for cognitive decline in Alzheimer's patients. The Committee encourages NINDS to treat Alzheimer's research as a high priority, and to continue to work closely with NIA and other research Institutes. (p. 136)

Action aken or to be taken:
Please refer to page NINDS - 37 of this document for NINDS response to this item regarding Alzheimer’s disease.

Positron Emission Tomography-The Committee is aware that positron emission tomography (PET) has been shown to identify Alzheimer's disease at a significantly earlier stage than other diagnostic methods. Earlier diagnosis of Alzheimer's allows for added treatment options which may delay the onset of the more debilitating aspects of this disease. The Committee urges NINDS, in collaboration with the National Institute on Aging and the National Institute of Mental Health, to expand its research into early diagnosis of Alzheimer's using PET imaging of the brain. (p. 136)

Action taken or to be taken:
Improving the tools for early diagnosis of Alzheimer’s disease and other degenerative disorders is an important focus of the mission of NINDS. To this end, NINDS is currently funding several studies that involve the development of improved imaging techniques in individuals with neurodegenerative diseases, including Alzheimer’s. One of these projects is 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. NINDS will also continue to seek collaborations with other ICs, such as the National Institute on Aging and the National Institute of Mental Helath, to facilitate research on PET scanning and other screening tools in Alzheimer’s Disease.

Batten Disease- The Committee is disappointed with the pace of research in Batten disease. The Committee believes that the Institute should actively solicit grant applications for Batten disease and also take aggressive steps to assure that a vigorous research program is established. In recent years, funding for this disease has decreased. The Committee strongly urges that increased funding be provided to combat this devastating disease. (p.137)

Action taken or to be taken

Batten disease has been, and continues to be, a research priority for NINDS. In an effort to stimulate this field of research, NINDS co-sponsored several workshops on Batten disease and related disorders between 1999 and 2000. These included both national and international researchers, and covered both broad and focused disease issues. In July 2000, NINDS participated in a joint program announcement to encourage scientists to apply progress in fundamental neuroscience to pediatric brain disorders, including Batten and related diseases. The Institute is currently sponsoring a wide range of research on Batten, 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 is also taking steps to overcome the common obstacles to gene therapy for many neurological diseases. In October 2000, NINDS co-sponsored a workshop on gene therapy, which focused in large part on storage disorders like Batten disease. In July 2001, NINDS responded to interest at this workshop by co-sponsoring a Request for Applications on gene therapy approaches to many diseases, including Batten disease and other genetic disorders.

Brachial Plexus Injuries - The Committee understands that injury to the nerves of the brachial plexus, which control the muscles of the shoulder, arm, elbow, wrist, hand, and fingers, can result in full to partial paralysis. While these injuries most often occur during the birthing process at a rate of 2-3 of every 1,000 births, traumatic injury is another cause. Although many affected individuals recover without intervention, and others can be helped with surgery, some experience permanent nerve damage. The Committee encourages NINDS to continue an aggressive program of nerve regeneration research, which should have benefits that can be applied to these injuries as well as other forms of damage to the peripheral and central nervous systems. (p. 137)

Action taken or to be taken

The goal of NINDS-supported nerve regeneration research is to better understand how damaged nerve fibers called axons can be stimulated to regrow and connect to their normal targets. Although some brachial plexus injuries can be repaired surgically, a better understanding of how to restore nerve function would undoubtedly contribute to the potential for full recovery after these injuries. Many NINDS-supported researchers are making progress towards this goal. For example, a number of NINDS grantees are evaluating the use of tissue and cell transplants, as well as bridges made of man-made materials, to reconnect damaged nerves. Other investigators are exploring how changes in gene expression can stimulate regeneration, and how inhibitory signals in the environment of the nervous system can be overcome. The application of growth-promoting factors is one therapeutic approach that continues to show positive results. Along these lines, NINDS-funded investigators recently demonstrated that a specific factor called fibroblast growth factor can be used to stimulate growth in an animal model of injury that

is similar to that which occurs at the brachial plexus. Importantly, this growth appeared to restore sensory function, but did not lead to symptoms of chronic pain, which is often a concern when abnormal growth of nerve fibers occurs. Other NINDS-supported laboratories are examining the use of assistive technology approaches, such as functional neuromuscular stimulation, to improve movement in people with weakened muscles. Although currently targeted to individuals with upper-level spinal cord injuries, these approaches may someday benefit individuals who have lost muscle function as a result of brachial plexus, or other nerve injuries.

Brain Tumor--The Committee is concerned that not enough attention is being given by NINDS to identifying causes of and treatments for brain tumors, and it encourages NINDS to continue working with NCI to carry out the recommendations of the recently issued Report of the Brain Tumor Progress Review Group. (p. 137)

Action taken or to be taken:
The NINDS continues to work with the National Cancer Institute (NCI), bringing together experts from several disciplines, to collaborate and share data on brain tumors. The Institute has begun to plan an initiative to investigate the blood-brain barrier. The blood-brain barrier is the cellular matrix that protects the brain from outside insults, but also prevents the entry of helpful therapeutic drugs, such as those that could be used against a tumor. We continue to be active in the brain tumor genome anatomy project (BT-GAP), and with NCI, have developed a first-generation gene-expression chip that might pave the way for new ways to diagnose brain tumor in patients. Additionally, the NINDS is supporting a number of basic biology research initiatives that include elements relevant to brain tumor.

ITEM: Congenital Muscular Dystrophy: to be submitted as a CACR.

Duchenne muscular dystrophy - The Committee is aware that NIH has been directed to intensify and enhance muscle disease research, and it urges NINDS to aggressively support translational research where possible. To accomplish this, the Committee strongly urges NINDS to establish no fewer than three centers of excellence for basic and applied research in the muscular dystrophies and encourages the Institute to provide sufficient funds for this purpose. The Committee expects NINDS to coordinate with NIAMS and the Centers for Disease Control and Prevention on the planning and activities for the centers of excellence. (p. 137)

Action taken or to be taken
NINDS, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the NIH Office of Rare Diseases (ORD), working together with private groups, held a "Workshop on Therapeutic Approaches for Duchenne Muscular Dystrophy" in May 2000. An international group of experts participated in this meeting along with representatives from patient groups and NIH staff. Following the workshop, the scientific organizers, topic leaders, and NIH program directors met to summarize the discussion and formulate future research priorities. In January 2001 NINDS and NIAMS issued a PA-S (program announcement with set-aside) to encourage research in areas these discussions highlighted as priorities for DMD research. The PA-S sets aside funds for the purpose of this research and does not restrict researchers to a single deadline for proposals. As directed by Congress, NINDS will work with

NIAMS and other components of NIH, as well as with the Centers for Disease Control and Prevention, to use all available mechanisms as appropriate, including centers, to enhance support for muscular dystrophy research.

Dystonia - The Committee is concerned that NIH has traditionally underfunded research to develop treatments for the neurological movement disorder dystonia. In light of the fact that it ranks as the third most common movement disorder behind Parkinson's and tremor, the Committee encourages NIH to afford substantial increased funding for additional research on both focal and genetic dystonia as it sets its priorities for fiscal year 2002. The Committee also continues to be interested in the expansion of NINDS's extramural research portfolio with respect to dystonia, and it encourages NINDS to continue to expand the study of the DYT1 gene. In addition, the Committee encourages the Institute to increase its collaboration with the dystonia research community in supporting epidemiological studies on dystonia and in increasing public and professional awareness of this disorder. (p. 138)

Action taken or to be taken
Please refer to page NINDS - 37 of this document for NINDS response to this item regarding dystonia.

Epilepsy. – The Committee believes that NIH should make finding a cure and effective treatments for epilepsy a priority. The Committee is encouraged by the development of 13 benchmarks for epilepsy research resulting from the March 2000 conference "Curing Epilepsy: Focus on the Future". The Committee encourages NIH to develop a plan to implement the research benchmarks, as the Director deems appropriate, including the funding projections needed to carry out the plan. The Committee directs that the plan be submitted Congress by April 1, 2002. Further, the Committee encourages the establishment of an Interagency Epilepsy Coordinating Committee comprised of agency scientists, industry, and patient representatives. (p. 138)

Action taken or to be taken
Please refer to page NINDS - 38 of this document for NINDS response to this item regarding epilepsy.

Multiple Sclerosis (MS)–Multiple sclerosis is a chronic, progressive disease of the central nervous system which is estimated to affect between 250,000 and 350,000 persons in the United States. While there is no known cure for MS, a number of therapies have been found helpful in slowing the disabling progression of the disease. The cause of MS remains equally elusive, although investigators are examining such factors as the role of viruses, genetics, and the environment. The Committee is aware that several scientific studies have not supported the role of trauma in causing MS or in triggering MS exacerbations. Nevertheless, the Committee is concerned over increasing reports or MS incidence caused by environmental triggers, be they allergic reactions, or more commonly, traumas such as automobile accidents. The Committee urges the Institute to devote additional resources toward study of the role of such traumas in causing multiple sclerosis. (p. 138)

Action taken or to be taken
It is very important to distinguish factors that may relate to the cause of the disease from those that might trigger an attack or produce symptomatic worsening. We know that symptoms of MS can worsen during stress; in fact, in patients with early disease, the worsening of subclinical symptoms may be the first clinical evidence of the illness. Under these conditions, it could be surmised that the stress had caused the disease. However, by using magnetic resonance imaging (MRI), we see evidence of disease on that predates the stress, indicating that the stress did not cause the illness. In the long term, efforts to determine the cause of MS will pay higher rewards than studies to identify factors that exacerbate symptoms. However, studies of factors that cause increased worsening should not be excluded.

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. It urges NINDS to expand its NF basic and clinical research portfolio through mechanisms such as requests for applications and program announcements. (P. 138)

Action taken or to be taken
Please refer to page NINDS - 41 of this document for NINDS response to this item regarding neurofibromatosis.

Prion disease - Britain and several other countries in Europe have documented transmissible forms of spongiform encephalopathies (TSEs) and variant Creutzfeldt-Jakob disease (vCJD), a type of TSE, caused by small infectious proteins called prions. It appears that the prions causing vCJD come from eating infected beef cattle. To date, NIH funding of prion-mediated diseases has been mainly for Creutzfeldt-Jakob disease (CJD–a separate but related disease to vCJD) but also has increased funding for bovine (cow) spongiform encephalopathy, scrapie (sheep spongiform encephalopathy) and chronic wasting (human). The Committee urges NINDS to specifically fund research into prion disease and to work with other agencies to detect the presence of disease. (p. 139)

Action taken or to be taken
NINDS research on prion diseases, beginning in the 1950's, laid the scientific foundation for understanding TSEs and for responding to the current public health concerns. NINDS intramural research first demonstrated that these diseases are transmissible; extramural researchers subsequently developed the prion theory of the cause of TSEs. The significance of these advances was acknowledged in the 1976 and 1997 Nobel prize awards respectively. In FY2000, the Institute, working with other components of NIH, began an extramural contract program to develop diagnostic tests, complementing intramural efforts in this area. In FY2001, the Department developed a comprehensive BSE/TSE Action Plan, including coordinated efforts from the NIH, the Food and Drug Administration, and the Centers for Disease Control and Prevention. NINDS is coordinating the NIH role, which expands scientific research on TSEs that affect humans and animals, including CJD, scrapie, BSE, and chronic wasting disease of deer and elk. NIH supported scientists, working closely with their European counterparts, are carrying out a broad program of research to understand the biological mechanisms of TSEs, devise diagnostic tests, and develop treatments and preventive measures.

Stroke–The Committee continues to regard research into the causes, cure, prevention treatment and rehabilitation of stroke as a top priority of the NINDS and of the NIH. Stroke remains the third-leading cause of death in the United States, a leading cause of permanent disability and a major contributor to late-life dementia. The Committee commends the NINDS for its efforts in beginning to develop a 5-year strategic stroke research plan. Expected to be released in the fall 2001, this plan will strongly stimulate novel ideas in stroke research. The Committee also encourages 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. 139)

Action taken or to be taken
In July, 2001, the NINDS held a meeting of 150 nationally and internationally recognized stroke experts to identify gaps in stroke knowledge, and set research priorities. The attendees were divided into panels in fifteen topic areas, including neuroimaging. The imaging panel report will define 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 comprehensive report from this meeting will serve as a plan to improve stroke prevention, diagnosis, treatment and rehabilitation, building on current knowledge and identifying new approaches.

Stroke in women - Stroke in women is a major health problem, with women representing 61 percent of all deaths from stroke. Stroke kills twice as many women as breast cancer and AIDS combined. The Committee is concerned that very little research has been directed toward understanding gender differences in stroke and cerebrovascular disease. Since the physiology of women's bodies is different from men's, stroke prevention and treatments may affect women in dissimilar ways. The Committee is pleased to learn that NINDS is funding a trial looking at whether postmenopausal hormone replacement therapy alters stroke risk. The Committee urges the Institute to increase research specifically in the area of stroke-related care, risk factors, preventive strategies, acute stroke management, aspects of post-stroke recovery and long-term outcomes among women. The Committee further urges the Institute to take steps to increase research into new therapies for stroke in women as well as ways of enhancing the vascular health of all Americans. (p. 139)

Action taken or to be taken:
Results of a significant clinical trial evaluating the impact of hormone replacement treatment on recurring stroke in menopausal women were announced in October, 2001. The Women's Estrogen for Stroke Trial (WEST), supported by NINDS, is the first randomized, controlled clinical trial of estrogen therapy for secondary prevention of cerebrovascular disease. Investigators found that estrogen hormone replacement therapy does not reduce the risk of stroke or death in postmenopausal women who have already had a stroke or transient ischemic attack.

The NINDS currently supports a trial that is comparing the efficacy of two procedures that unblock a clogged carotid artery in the neck, a significant risk factor for stroke: Carotid endarterectomy and carotid stenting. One facet of the trial will examine gender differences in these procedures. Previous research has shown that women may not benefit from carotid endarterectomy as much as men do.

Another ongoing trial studying the epidemiology of the "stroke belt" will also document gender differences.

NINDS stroke clinical trials have appropriate numbers of women enrolled enabling subgroup analysis in order to detect significant gender differences.

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Epilepsy – The conferees understand that over two million Americans suffer from epilepsy, with one million suffering from uncontrolled seizures. The conferees are interested in the acceleration of epilepsy research and encourage NINDS to take steps to jumpstart promising epilepsy research areas. In particular, the conferees urge NINDS to establish an annual lectureship in the epilepsy research field to provide the intellectual stimulation to prompt new findings in both the NINDS intramural program and the extramural community. The conferees request that NINDS consider naming the lectureship in memory of Judith Hoyer. Mrs. Hoyer had epilepsy; she spent her life helping families dealing with the condition and promoting research into a cure and a better quality of life for those with epilepsy. Such a lectureship would continue her legacy of stimulating important epilepsy research. (p. 90)

Action taken or to be taken

NINDS is committed to both understanding the causes of and developing effective therapies for all forms of epilepsy. The Institute currently supports a large number of research projects aimed at preventing, treating, and eventually curing epilepsy. These include projects investigating the mechanisms of seizure onset in the developing brain, the effects of seizures on children's cognitive, emotional and behavioral development, and the relationship of hormonal fluctuations in females to epileptic changes in the brain, including two clinical trials. NINDS also supports epidemiology studies of the rates of epilepsy in the elderly, and 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, 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 trial portfolio is growing and encompasses a wide range of approaches to treating the disorder. In addition to the trials mentioned above, these includes two surgical protocols, one involving the use of radiosurgery ("gamma knife") in treating mesial temporal sclerosis and, the other, electrical stimulation of the anterior nucleus of the thalamus as a novel treatment. Other trials include an investigation of the efficacy of the ketogenic diet, a pilot study of neurosysticercosis treatment, and treatment of depression.

The NINDS continues to sponsor the Therapeutics Research Program which supports preclinical studies of antiepileptic drugs. Since 1975, the program has evaluated well over 20,000 compounds for their anti-convulsant properties, and a number of identified compounds are now in clinical use.

In March 2000, NINDS, together with the Epilepsy Foundation, the American Epilepsy Society, Citizens United for Research in Epilepsy (CURE), and the National Association of Epilepsy Centers, jointly sponsored a White House - initiated Conference "Curing Epilepsy: Focus on the Future." The conference galvanized the epilepsy research community to not just focus on treating the symptoms of epilepsy, but rather to look forward and focus on actually curing epilepsy (defined as "preventing epilepsy in those at risk and no seizures, no side effects in those who develop the disorder"). A major outcome of the meeting was the development of 13 research benchmarks that 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 already begun to implement several of these benchmarks, including holding workshops on "Models of Epileptogenesis and Epilepsy" and "Antiepileptic Drug Monotherapy Indications" (both held in March 2001) and planning a workshop on "Molecular Analysis of Complex Genetic Epilepsies", to be held January 31 - February 1, 2002. In addition, NINDS is actively working with epilepsy researchers and advocates to develop an overall plan to implement the benchmarks, beginning with a planning meeting held in December 2001.

In addition to these activities, NINDS plans to establish an annual lectureship in the epilepsy research field to honor the memory of Mrs. Judith Hoyer. The Institute agrees with the conferees that this lectureship would be a fitting tribute to the life of Mrs. Hoyer. The Institute program staff will consult with intramural staff, the extramural research community, and the advocacy community to decide on the best structure for this lectureship. It is anticipated that the inaugural lecture will take place later this year.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2001 Amount Authorized	2002 Estimate	2003 Amount Authorized	2003 Budget Estimate 1/
Research and Investigation	Section 301	42§241	Indefinite	$1,305,135,000	Indefinite	$1,416,093,000
National Institute of Neurological Disorders and Stroke	Section 417B	42§285	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	26,513,000	b/	27,299,000
Total, Budget Authority				1,331,648,000		1,443,392,000

a/ Funding provided under the Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2002 (P.L. 107-116).
b/ Reauthorizing legislation will be submitted.

1/ Reflects proposed transfer from the National Cancer Institute

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
Office of the Director	71	72	72
Division of Extramural Activities	114	127	126
Division of Intramural Research	404	419	418
Total, NINDS	589	618	616

Statutorily-ceiling exempt FTEs not included above

Funds to support these FTEs are provided by Cooperative Research and Development

FISCAL YEAR	Average GM/GS Grade
1999	10.2
2000	10.4
2001	10.3
2002	10.4
2003	10.5

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1994	$590,065,000	$630,650,000	$630,650,000	$630,650,000
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				(408,000)
2003	1,443,392,000			

1/ Reflects enacted supplements, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activites 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
5/ Reflects a decrease of $2,457,000 for the budget amendment for Bioterrorism.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
Detail of Positions

GRADE	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
ES-6	0	0	0
ES-5	2	3	3
ES-4	4	3	3
ES-3	0	0	0
ES-2	0	0	0
ES-1	0	0	0
Subtotal	**6**	**6**	**6**
Total - ES Salary	$1,604,400	$1,677,009	$1,749,618
GM/GS-15	42	44	44
GM/GS-14	39	42	42
GM/GS-13	50	56	56
GS-12	66	70	70
GS-11	71	71	71
GS-10	8	8	8
GS-9	49	50	50
GS-8	26	25	25
GS-7	41	43	42
GS-6	10	15	15
GS-5	10	10	10
GS-4	15	15	15
GS-3	2	2	2
GS-2	2	3	3
GS-1	1	0	0
Subtotal	**432**	**454**	**453**
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade	6	6	6
Senior Grade	5	5	5
Full Grade	1	1	1
Senior Assistant Grade	1	1	1
Subtotal	13	13	13
Ungraded	166	174	173
Total permanent positions	451	473	472
Total positions, end of year	617	647	645
Total full-time equivalent (FTE) employment,end of year	589	618	616
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$133,700	$139,783	$144,186
Average GM/GS grade	10.3	10.4	10.5
Average GM/GS salary	$63,677	$66,733	$69,936