FISCAL YEAR 2005

Justification of Appropriation

Estimates

National Institutes of Health

National Institute of Neurological Disorders and Stroke

February 2, 2004

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

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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, [$1,510,776,000]*$1,545,643,000.*

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Omnibus Consolidated Appropriations Act for Fiscal Year 2004]

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:

FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
608	$1,455,090,000	596	$1,500,693,000	595	$1,545,623,000	(1)	$44,930,000

This document provides justification for the Fiscal Year 2005 activities of the National Institute of Neurological Disorders and Stroke (NINDS), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2005 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

The Mission: The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disorders by discovering ways to prevent or to treat these diseases.

The Burden of neurological disorders: Neurological disorders afflict people of all ages, in all segments of society. They may affect the brain, the spinal cord, the sensory nerves that convey information about the world to the brain, the motor nerves that activate muscles and glands, and the autonomic nervous system, which regulates "fight or flight" reactions and body functions as fundamental as the beating of the heart and the activity of the digestive system. Many diseases of the nervous system are fatal; others result in years of chronic disability and suffering. They disrupt essential bodily functions, cause pain and discomfort, and impair vital abilities, from perception and movement, through emotions, memory, language, and thinking.

Stroke, chronic pain, and brain trauma are among the most common causes of disability and premature death in the United States. Alzheimer's, Parkinson's and other neurodegenerative diseases are becoming increasingly prevalent as our population ages. Autism, brain tumors, cerebral palsy, congenital nervous system defects, and epilepsy are a few of the many nervous system problems that can strike in early life. Multiple sclerosis, brain trauma, and spinal cord injury are among those that commonly afflict young adults. There are hundreds of other nervous system disorders, many unfamiliar to most Americans until a family member is affected. The cumulative impact of nervous system disorders, common and rare, is enormous.

The NINDS Strategy: To carry out its mission, NINDS supports a spectrum of research, from fundamental investigations of how the nervous system develops, works, and goes awry in disease, through efforts to translate the insights from basic research into potential treatments and prevention strategies, and finally, to clinical trials to test the safety and efficacy of interventions. The Institute must pay particular attention to basic research, the training of new investigators, and rare diseases, which are unlikely to attract private investment. Because diseases do not respect the boundaries that divide institutes and agencies, government and the private sector, and the United States from other countries, the NINDS works together with other components of the NIH to address issues that go beyond the mission of NINDS alone, and cooperates with other organizations that share the goal of combating neurological disorders.

The *NINDS extramural research program*, which comprises the majority, about 88 percent, of the Institute's efforts, supports research by physicians and scientists at universities, medical centers, research institutes, and companies throughout the U.S. The extramural program relies heavily upon the collective wisdom and ingenuity of our nation's research community to help monitor research needs, seek out scientific opportunities, propose new projects, evaluate proposals, carry out the research, and plan for the future. The diverse needs of neurological disorders are especially suited to the NIH system for fostering high quality investigator-initiated scientific research. When appropriate, the Institute also actively stimulates scientific interest in specific areas through planning efforts, workshops, and grant and contract solicitations.

The *NINDS intramural research program,* on the NIH Bethesda, Maryland campus, is one of the largest neuroscience research centers in the world, with unique advantages that complement the extramural programs and a distinguished history of accomplishment. The NIH John Edward Porter National Neuroscience Center, due to open its first stage in June 2004, aims to expedite progress against neurological diseases by overcoming artificial disciplinary boundaries within and across NIH institutes and setting the standard for collaborative research in neuroscience.

Progress: The complexity of the brain, its limited capacity to repair itself, the multiplicity of neurological disorders, and the protective blood-brain barrier, which excludes most potentially therapeutic agents, challenge the best efforts of medical science to treat brain disorders. Progress is often won in small increments, but the cumulative advancement is having a major impact on people confronting neurological disorders. The first treatments—albeit still far from adequate—have proven effective for reducing damage from stroke and spinal cord injury. Immune therapies

decrease symptoms and slow the progression of multiple sclerosis. Surgical options have become available for treating Parkinson's disease and epilepsy, complementing the gradual improvements in drug therapy. New drugs have also emerged for other conditions, such as headache. Enzyme therapies have brought the first successes in treating Gaucher and Fabry diseases, and demonstrate the potential for treating the many other inherited enzyme deficiency disorders, such as the mucopolysaccharidoses. Neural prosthetic devices improve quality of life for some people with paralysis from spinal cord injuries. Molecular genetics and brain imaging are augmenting clinicians' insight to diagnose the bewildering array of diseases and guide therapy. Advances in prevention are also notable--this year alone almost a quarter of a million fewer deaths from stroke will occur than would have without progress in prevention. Prevention of nervous system birth defects, such as spina bifida, and genetic counseling for inherited disorders, such as Tay-Sachs disease, are also having a major impact on public health.

Promise for the future: For many neurological disorders, the best available interventions only partly alleviate symptoms and fail to halt the progression of disease. However, the prospects for the future are encouraging. New prevention and treatment strategies under development include highly specific drugs that home in on the molecules that cause disease, stem cell therapies that repair the damaged nervous system, natural neurotrophic factors that promote survival and growth of brain cells, "vaccines" that prevent stroke, implantable deep brain stimulation devices that compensate for brain circuits unbalanced by disease, modulators that ameliorate autoimmune disorders, therapies that repair or replace defective genes, neural prostheses that read control signals directly from the brain, and behavioral interventions that encourage the "plasticity" of the brain and spinal cord to compensate for damage.

Scientific Advances: *Understanding the nervous system in health and disease*

The progress to date and the promising new strategies on the horizon build upon decades of fundamental discoveries about how the nervous system develops, performs its functions, and malfunctions in disease. Our knowledge of stem cells and neurotrophic factors emerged from basic studies of brain development. Deep brain stimulation therapies rely upon understanding of how brain circuits control movement, as do neural prosthetic devices that interface with the brain or spinal cord. Gene therapy, new understanding of what causes disease, diagnostic tests, and animal models that mimic human disorders and expedite testing of therapies are among the fruits of studies in neurogenetics. Research on the underlying causes of many neurological disorders are converging to show that similar mechanisms come into play at the level of cells and molecules. So, success in targeting critical molecular steps of free radical damage, "cell suicide," protein accumulation, inflammation, and other common disease processes in any one disease is likely to present opportunities for other diseases as well. Look closely at the origins of any therapeutic strategy, and the essential role of basic research on the healthy and diseased nervous system becomes apparent. For this reason, NINDS supports a wide range of research, from molecules to behavior, in the normal and diseased nervous system. The following recent advances illustrate:

• Scientists have developed methods to watch how even the finest branches of nerve cells change over time–from minutes to months–in the brains of living mice. Genetically engineered mice display fluorescent markers that light-up particular types of nerve cells, and new microscopy techniques reveal the details of the cells within the brains of living animals. These technical advances are helping to answer pivotal questions about how genes and experience shape the nervous system in development, and how the brain adapts throughout life.

• Research on understanding neural stem cells from several sources is advancing rapidly, as a sampling of recent findings illustrates: Investigators have isolated cells from the white matter of adult human brain removed for therapeutic surgery that can multiply and specialize to form all of the major cell types of the brain. Other scientists have found that the signaling chemical nitric oxide (NO) turns off the production of new nerve cells, and that suppressing NO can increase the generation of cells within the brain of adult mammals. Another study suggests that stem cells from very young mice are immune privileged, that is, the cells are not rejected when transplanted into mice that are not closely related. Researchers studying regulatory systems that control the proliferation of embryonic stem cells discovered a protein called "nucleostemin" that not only helps regulate the proliferation of stem cells, but also plays a critical role in the proliferation of cancer cells. Recent findings show that cells from bone marrow may be capable of fusing with brain cells, perhaps activating genes usually specific to brain cells, and helping to repair damage.

• Paradoxically, people who suffer a major stroke may have less brain damage if they have previously experienced a minor stroke. Using gene microarray technology, scientists monitored the activity of thousands of genes in a mouse model of stroke that mimics this protective effect. They found striking similarities to the changes that hibernating animals undergo to cope with the lowered blood flow and oxygen supply. Therapies that capitalize on these natural brain protective mechanisms might be particularly valuable in people at high risk for stroke.

• The first published data from the NINDS Gene Expression Nervous System Atlas, or GENSAT, project is providing remarkable information about where and when genes are active in the brain, which will help answer a wide range of questions about how the brain develops, works, and goes wrong in disease. GENSAT is an ambitious project that aims to map the activity of thousands of genes in the brain and to provide genetically engineered mouse strains that allow scientists to classify, observe, and track brain cell types according to molecular characteristics and function, rather than by their appearance alone. For example, a mouse strain from one of the first 150 genes studied allowed scientists to follow cells that activate the gene *Gscl,* which is missing in people who inherit DiGeorge syndrome - a rare congenital disease whose symptoms include a history of recurrent infection and heart defects - alerting researchers to a connection with the rapid eye movement (REM) phase of sleep in this disease. Other strains helped reveal how developing nerve cells and nerve fibers find their way in the developing brain. The GENSAT data will be made publicly available through the NIH's National Center for Biotechnology Information (NCBI), and thereby constitute an unprecedented resource for neuroscience research.

• Researchers investigating a rare familial form of early-onset Parkinson's disease discovered that too many copies of the *normal* alpha-synuclein gene may cause Parkinson's disease, and provided major clues into the process by which Parkinson's disease develops. Abnormal accumulations of the protein alpha-synculein also occur in the brains of people with common types of Parkinson's and Alzheimer's disease. Other proteins accumulate in inherited ataxias, Huntington's, ALS, and several other disorders. This findings adds to evidence that improper disposal of proteins by brain cells is a factor in several neurological disorders.

• Researchers have identified a gene that apparently modifies the age of onset for both Parkinson's and Alzheimer's diseases. How variations in the gene, GSTO1, might affect disease timing is not yet clear, but the finding may lead to therapeutic approaches to delay the onset or progression of Alzheimer's and Parkinson's disease.

• Scientists have discovered that defects in the protein dysferlin, which have been implicated in limb-girdle muscular dystrophy type 2b and Miyoshi myopathy, do not make muscle cells more easily damaged than normal cells, as in other forms of muscular dystrophy. Instead the defects disable the cells' normal capacity to patch damage from the everyday stresses of muscle use. Dysferlin is the first identified component of muscles' membrane repair machinery.

• Results from the first-ever autopsy study of brains from people with restless legs syndrome (RLS) suggest that this common disorder may result from inefficient uptake or storage of iron in certain brain cells. The findings provide a possible explanation for this disorder and may lead to new ways of treating the disease.

• Scientists have long known that the loss of motor neurons, the nerve cells that activate muscles, is responsible for ALS, but why these cells die remains a mystery. Genetically engineered mice with a mutation that can cause human ALS show that the cause may lie not in the motor neurons themselves, but in neighboring supporting cells, which may have implications for treatment.

• Research on mice genetically engineered to lack the protein GIRK2 suggests that males have a natural pain control system that isn't operating in females, possibly helping to explain why women are more sensitive to pain than men and get less relief from some pain relieving drugs.

• Mood, attention, and higher thought processes can alter how painful a given stimulus feels. A new study in rats reveals how a small area of the cerebral cortex, called the insula, can increase or decrease perceived pain thresholds, showing that the cerebral cortex is not only the ultimate seat of pain perception, but also adjusts the sensitivity to painful stimuli in a top-down manner.

Scientific Advances:
Translating scientific progress into treatment and prevention of nervous system disorders

Translating advances in understanding the healthy and diseased nervous system into better ways of treating and preventing neurological disorders is vital to the NINDS mission. Years of

painstaking research refines a new idea in the laboratory, tests a potential therapy in animals, and then evaluates safety and efficacy through a series of clinical trials of increasing size and complexity. The interactions between the lab and the clinic are two-way, with insights from clinical studies often opening new avenues for laboratory research. The Institute funds research at every step of this pathway. Interventions based on drugs, surgery, gene therapy, vaccines, immune system modulators, behavior, diet, neuroprosthetic devices, and cell or tissue transplantation are among those under development. The following recent findings highlight translational and clinical research on diagnosis, treatment, and prevention:

• By introducing a mutant form of the gene alpha-synuclein, which can cause Parkinson's disease in people, researchers have developed a primate model that mimics human Parkinson's disease in its slowly progressive time course of damage to specific areas of the brain. This model offers new opportunities for studying the mechanisms of disease and exploring new therapies.

• Fragile X syndrome is the most common inherited cause of mental retardation. People who carry a less severe form of the fragile X gene defect have a poorly understood progressive neurodegenerative disease. Scientists developed a fruitfly model of this disease and found abnormal clumps of proteins in the degenerating fly nerve cells that resembled those seen in several human neurodegerative diseases. Increasing the level of another protein that helps prevent the clumps suppressed neurodegeneration. Fly models of Parkinson's and Alzheimer's diseases have similarly brought the powerful experimental methods developed for studying fruit flies to bear on neurodegenerative disorders.

• A new diagnostic test for Duchenne muscular dystrophy will eliminate the need for painful muscle biopsy in many children, and help identify female carriers of the disease before they pass it on to their sons. The method, called "single condition amplification/ internal primer" or SCAIP, should allow the development of tests for other large genes. Initial results of a new diagnostic test for myotonic dystrophy type 2 indicate that this disease is much more common than previously thought and may be one of the more common forms of muscular dystrophy. The test will allow researchers to fully describe the clinical features of this disease for the first time.

• A new study using a cutting edge research technique called "proteomics protein fingerprinting" shows that HIV patients with dementia have distinct protein patterns in their blood, setting them apart from patients with no symptoms of dementia. The study suggests a possible way to screen HIV patients for the first signs of cognitive impairment.

• Cells from gliomas, the most common type of brain tumor, often migrate within the brain, avoiding surgery, radiation, and drugs. Two studies in mice suggest that neural stem cells can seek out these evasive glioma cells and effectively deliver therapeutic agents. There are many challenges before this strategy is ready for people, but the encouraging results present yet another possible therapeutic use of stem cells.

• Researchers have demonstrated that transplantation of dopamine nerve cells derived from somatic cell nuclear transfer (SCNT) can help treat a Parkinson's disease-like condition in mice - the first time SCNT has been used for a brain disease. In SCNT, the nucleus from an adult cell is

transferred to an egg cell, which then forms stem cells that generate cells which can be used therapeutically.

• In "dominantly" inherited diseases, a single mutated copy of the relevant gene, from either parent, causes disease, despite the presence of a normal copy of the gene from the other parent. Scientists working in cell culture models of Machado-Joseph disease (spinocerebellar ataxia type 3) and an inherited form of dementia (frontotemporal dementia) have successfully addressed this type of gene defect. They used a method called RNA interference to turn off a harmful inherited mutant gene, while allowing the normal copy of that gene to remain active.

• Spinal muscular atrophy (SMA) is an inherited neurodegenerative disease, which in its most severe form is fatal in infancy. Researchers studying cultured cells from people with SMA found that valproic acid, a drug commonly used to treat epilepsy, can increase the amount of the critical protein that is lacking in SMA, providing a possible lead for development of a treatment.

• An NINDS clinical trial established the clot busting drug tPA as the first emergency treatment proven effective in improving the outcome from stroke, but the effectiveness of tPA is limited by side effects that can be toxic to nerve cells. Scientists, returning to the lab, have now discovered that at least part of this toxicity arises from increased activity of brain enzymes that degrade the "extracellular matrix' in which brain cells are embedded. Targeting this harmful process may offer a new approach for improving stroke therapy.

• The NINDS, working closely with voluntary disease groups, developed a consortium of 26 laboratories to screen a set of 1040 drugs for potential use against neurodegenerative diseases. Most of these drugs are approved by the U.S. Food and Drug Administration for other uses, so they might move more quickly toward clinical trials. The Consortium is sharing data on 29 laboratory screening tests based on molecules, cells in culture, or simple organisms such as fruit flies that are relevant to diseases such as Parkinson's, Huntington's, ALS, and SMA and to mechanisms of neurodegeneration common to several disorders. Several promising drugs have moved to further testing in animal models of diseases. Potential drugs include, for example, antibiotics that were effective in multiple assays for ALS, and a natural compound that showed promise in tests relevant to several inherited diseases that share a common mechanism.

• The International Study of Unruptured Intracranial Aneurysms (ISUIA) has provided substantial new information that helps predict which people with a brain aneurysm are likely to benefit from surgical repair, and which are likely to be better off with careful monitoring and avoiding the risk of surgery. This should enable treatment choices that will reduce the death and disability resulting from brain aneurysms.

• The African American Antiplatelet Stroke Prevention Study (AAASPS) showed that aspirin is as effective as ticlopidine for prevention of a second stroke in this population. For those who can tolerate it, aspirin is readily available, less expensive, easier to use, and has less potential for serious side effects than ticlopidine.

• A new study shows that subarachnoid hemorrhage, an often fatal type of stroke, may be largely preventable in young and middle aged men and women because the most important risk factors–cigarette smoking, hypertension, and illicit drug use–can be modified by behavioral change or medication.

Brain Plasticity–A Story of Discovery

In 1913, Santiago Ramón y Cajal, one of the most influential neuroscientists of all time, wrote of the brain and spinal cord: *"….once the development was ended, the founts of growth and regeneration of the axons and dendrites [nerve fibers] dried up irrevocably. In adult centers the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree."*

For most of the last century, this pessimism reigned. The intricacy of the brain, its apparent reluctance to repair itself, and the spate of discoveries about how genes influence the brain might seem to reinforce that deterministic view. In the last decade or two, however, "the science of the future" has begun to emerge. Mounting evidence, much of it from NIH supported studies, shows that the adult human brain can change – indeed that change, or *brain plasticity,* constantly occurs. This new way of looking at the nervous system is providing insights into what causes disorders and how to treat them.

Technologies that Cajal could only dream of helped drive the revolution in understanding brain plasticity – imaging of brain activity in people as they perform different tasks, microscopy techniques that reveal the fine branches of nerve cells in living mouse brains, methods to monitor the electrical activity of single nerve cells and the strength of synapses, and many others. No single finding gave rise to the sea change in how scientists view the brain. Among the many findings contributing: the fundamental "maps" that represent our body in the brain are not fixed, but adjust with experience, as we learn new skills or our body changes; nerve fibers in the adult brain and spinal cord *can* grow under properly permissive conditions; and even the brains of 60 year old humans *do* make new nerve cells. While once the adult brain seemed static, we now know that the brain's detailed structure and function is dynamic, constantly adapting to changes in the body and the external world.

It is perhaps obvious that brain plasticity provides tremendous advantages, enabling us to learn, to adapt to our changing environment, and to compensate for many problems from disease, trauma, or aging. But plasticity, for all its benefits, has costs as well. The same cellular and molecular mechanisms that allow adaptive changes can, under some circumstances, contribute to brain disorders. For example, plasticity helps when it allows experience to alter the "maps" by which the brain controls muscles and represents the sensory input from the body, contributing to the learning of new skills – so that the map representation of the fingers may expand as we learn to play the piano. However, in trying to adjust to repetitive practice on a musical instrument, writing for long periods, or repeated workplace movements, brain plasticity can sometimes produce deranged connections in sensory or movement control areas of the brain that result in dystonias – painful and disabling involuntary muscle contractions. Another trade off is inherent in the brain's ability to strengthen neural pathways based on experience. We learn, usually to our benefit, when nerve cells that are highly active in the task at hand strengthen the synapses by which they influence one another's electrical activity. However, the same capacity to adjust synapses can cause problems, such as chronic pain conditions, when pain circuits in the spinal cord are activated strongly enough to strengthen synapses along pain sensing nerve pathways and increase sensitivity to pain. A most remarkable example of brain plasticity is the astonishing extent of recovery by some children after half of their cerebral cortex is surgically removed by "hemispherectomy," a last resort used to stop very severe and otherwise untreatable epilepsy. Plasticity comes into play in many ways during epilepsy. Over excitation of nerve cells during a seizure may strengthen brain circuits, provoke release of growth factors, elicit "sprouting" of new nerve branches, alter neurotransmitter systems, and even stimulate birth of new nerve cells. Some of these changes undoubtedly help the brain compensate for epilepsy, but others apparently contribute to its progression.

The insights about brain plasticity are yielding novel strategies to treat or prevent neurological disorders. For hand dystonias, sensory and movement exercise programs designed to reverse the harmful changes in brain maps are

showing promising results in early trials. "Pre-emptive analgesia" to block activity of pain pathways in the spinal cord during some types of surgery may minimize chronic pain resulting from strengthening of pain circuits. By observing the brain reorganization that allows some people to slowly recover perception and movement following stroke or brain trauma, scientists have devised behavioral approaches to encourage this adaptive brain plasticity. "Constraint-induced therapy," which compels stroke victims to use their affected limbs, thereby overcoming maladaptive brain changes from non-use and inducing favorable use-dependent brain reorganization, has shown enough promise that phase III clinical trials are underway. Insights about plasticity are also being applied in novel rehabilitation programs for people with spinal cord injuries, through body-weight-supported treadmill walking and other procedures designed to retrain spinal cord circuits. A long-standing NINDS program to develop drugs for epilepsy, informed by the recognition that plasticity can contribute to epilepsy, is now working to develop animal models of "epileptogenesis" to screen for drugs that will prevent changes in the brain that give rise to epilepsy or drive its progression. Another encouraging line of research, which may have implications even for people with no neurological disorder, shows that behavioral experiences as simple as exercise can stimulate growth of new nerve cells and connections in the adult brain. As we learn more about what controls brain plasticity, we may learn to enhance our "cognitive reserve" capacity, and stave off cognitive problems that often accompany aging.

Although Cajal later softened his pessimism about growth of nerve fibers in the adult brain and spinal cord, he would have been astounded by recent findings that the brains of mature humans produce new nerve cells. Scientists have even isolated neural stem cells from brain tissue removed at autopsy or during therapeutic surgery that can divide and specialize to form all of the major cell types of the brain. Animal experiments suggest that the new cells seek out areas of brain damage, and scientists are identifying natural signals that control the formation, specialization, and migration of the cells. Drugs, such as the statins used to treat high cholesterol, appear to stimulate plasticity and hasten recovery in animal models of stroke. Perhaps a combination of drugs and behavioral rehabilitation programs will someday maximize recovery from stroke, trauma and other brain disorders. Together with progress in identifying the factors that normally suppress growth of nerve fibers in the brain and spinal cord, and promising animal experiments transplanting stem cells from various sources for Parkinson's, ALS, stroke, trauma, inherited diseases, and multiple sclerosis-like conditions, these results present a tantalizing indication of the future. However, as researchers work towards applying these strategies in people, they must be mindful of the possibility of doing harm, for example by evoking chronic pain through inappropriate new synapses or brain tumors through unconstrained growth.

Oliver Wendell Holmes, an American contemporary of Cajal, famously said "Man's mind stretched by a new idea never goes back to its original dimensions." He was speaking perhaps more as a philosopher than a professor of anatomy and physiology – although he wore both hats; nonetheless, the aphorism seems appropriate to insights about brain plasticity. Just as the brain adapts to experience, scientists are stretching their own minds to encompass the new ideas about the capacity of the brain to change. We have seen the first glimpses of how knowledge of brain plasticity can help treat or prevent neurological disorders, and the potential for the coming years is enormous.

NIH Roadmap

Every component of the NIH Roadmap has potential to advance the treatment and prevention of nervous system diseases. The "New Pathways to Discovery" theme contains a Structural Biology initiative focused on protein structure that illustrates this potential:

All that the nervous system does depends on communication between nerve cells, but each cell, like all cells, is isolated by a membrane that separates it from other cells and the environment. So, those critical conversations between nerve cells depend on chemical messengers called neurotransmitters, "receptor" proteins in the membrane that detect neurotransmitters, and ion channels, which span the membrane and act as tiny molecular "switches" that control the flow of ions into and out of cells. Ions are the electrically charged molecules, such as the positive sodium and negative chloride of dissolved table salt, that carry electric currents in the body.

Some nervous system disorders, such as inherited forms of epilepsy, muscular dystrophy, and movement disorders, arise directly from a gene defect in ion channels or receptors themselves. In other diseases, such as myasthenia gravis, a person's own immune system can attack these proteins. In most common neurological problems, even stroke and trauma, the activity of receptors and channels is somehow involved.

Not surprisingly, most drugs now used to treat neurological disorders act, either directly or indirectly, on membrane proteins, such as ion channels and receptors. Determining the three-dimensional structure of nerve cell membrane proteins is critical for understanding how they work and for developing better drugs. However, because these proteins are deeply embedded in a fatty cell membrane, this has been extremely difficult. A major goal of the structural biology Roadmap is to develop methods that will enable scientists to produce large enough quantities of individual mammalian membrane proteins, such as ion channels, to generate pure protein crystals that will allow researchers to determine their precise three dimensional structure. This will have enormous benefits for many neurological disorders in the future.

NINDS Initiatives

With the guidance of the National Advisory Neurological Diseases and Stroke (NANDS) Council, NINDS continues its emphasis on investigator-initiated research, as is appropriate to the challenges posed by the diversity of neurological diseases. The Institute tailors programs to serve the different needs of basic, translational, and clinical research and engages in directed initiatives when public health needs dictate, unusual scientific opportunities arise, a central resource can best address a common need, bottlenecks to progress warrant a more active approach, or mandates must be addressed, such as goals under the Government Performance and Results Act (GPRA). The following highlight some new initiatives and enhancements to ongoing programs:

Clinical Trials for Neurological Disorders: Scientific progress is bringing increasing opportunities for clinical trials. To facilitate clinical trials and manage them effectively, NINDS has implemented grant mechanisms for planning trials and for pilot trials; developed procedures to optimize trial design; enhanced peer review procedures; increased professional staff to support trial design and monitoring; improved databases for tracking of trials; developed a website to help investigators develop clinical trials applications, including a "Toolkit," of resources and guidelines on design, implementation and oversight; supplemented clinical trials to collect DNA samples for the recently established NINDS Human Genetics Repository; and created a subcommittee of the NANDS Council to provide broad programmatic and priority-setting advice on Institute clinical research activities, including clinical trials. Clinical trials for neurological disorders will benefit also from the NIH Roadmap initiatives for "Re-engineering the Clinical Research Enterprise," which address critical issues that go beyond the mission of neurology alone, such as harmonizing requirements related to clinical research among government agencies.

Ongoing clinical trials, in both intramural and extramural divisions, target prevention and treatment. Studies range from planning, through early phase investigations, to large phase III multi-center projects. Trial interventions include many modalities, such as drugs, surgery, gene transfer, chronic deep brain stimulation, cell transplantation, hypothermia, radiosurgery,

immunotherapy, vaccines, behavioral management, physical therapy, and psycho-social methods. New or ongoing trials focus on a wide variety of disorders, including attention deficit hyperactivity disorder (ADHD), AIDS, ALS, autism, brain tumor, Canavan disease, cerebral palsy, dystonia, epilepsy, essential tremor, migraine, multiple sclerosis, post-herpetic neuralgia, pain, Parkinson's disease, sickle cell disease, stroke and traumatic brain injury.

While continuing to expand support for individual trials, NINDS is developing a clinical trials network that will encompass the greater community of neurologists. The Clinical Research Collaboration (CRC) will engage hundreds of community practice-based and academic-based neurologists to speed trials; minimize costs; make trials more accessible to patients; facilitate the recruitment of a diverse spectrum of participants; enable more trials of rare diseases; and improve the transfer of research results to clinical practice in community settings.

Training is another major requirement for clinical trials, especially as the CRC gets underway. For FY 2005, the Institute is developing an intensive five-day course to train junior neurology and neurosurgery faculty and fellows in the design and conduct of clinical trials. Through this and other efforts, the NINDS will develop a cohort of neurology and neurosurgery clinical investigators with the training essential to participating in well-designed, multidisciplinary clinical investigations in neurological disorders.

Biomarkers: Biomarkers are observable indicators of specific biological or disease processes, or of responses to a therapy. Brain imaging, for example, is accepted as a valid indicator of disease progression in multiple sclerosis, which has revolutionized the ability to test new therapies for this disease. The development of valid biomarkers for other neurological disorders would expedite clinical trials. In FY 2005, the NINDS will hold a series of workshops to identify and prioritize the challenges and needs in this area, and starting in FY 2006, will issue solicitations to invite basic and clinical research applications to develop biochemical, cellular, physiological, or genetic markers that can be used to predict risk, aid in early diagnosis, assess disease progression, or be used as surrogate outcome measures in clinical trials to test new therapeutic agents.

Translational research: Translational research encompasses the many steps that are needed to move from basic research insights to a therapy that is ready for human testing in clinical trials. The NINDS has a long history of programs in this arena, but scientific progress is increasing opportunities for translational research. The NINDS has responded by developing a comprehensive research program, with peer review criteria tailored to the needs of translational research and milestone driven funding, which is common in industry. In FY 2003, the Institute funded the first projects in this program, which explore drug, stem cell, and gene therapy for diseases such as ALS, brain tumor, epilepsy, Huntington's disease, Parkinson's disease, tuberous sclerosis, traumatic brain injury and stroke. The Institute developed the program with the expectation that translational research will grow to a level appropriate to the scientific opportunities arising, and continued expansion is anticipated in FY05. Complementing the broad translational program are several specific NINDS efforts. Among these:

• Spinal muscular atrophy (SMA) is the focus of an innovative contract-based approach, initiated in FY 2003, to expedite the development of therapies. In the last few years, the discovery of the

gene defects responsible for SMA and the development of animal models that mimic the human disease, as well as the impact of the disease on patients and families, have made SMA an excellent candidate for such an approach. The first research projects are expected to be funded in the second quarter of FY2004. If successful, this approach might be applied to other diseases.

• For nearly three decades, the NINDS Neural Prosthesis program has fostered the development of electronic and mechanical devices that connect to the nervous system, and help compensate for abilities lost through disease or injury. For FY 2005, the Institute is continuing efforts to benefit people with spinal cord injuries, as well as projects to improve technology for deep brain stimulation therapy and to develop neuroprostheses controlled directly by the brain.

• Since 1975, the NINDS Anticonvulsant Screening Project (formerly part of the Antiepileptic Drug Development Program) has worked with industry to test more than 20,000 compounds for their anti-convulsant properties, including several drugs now in clinical use. Guided by the epilepsy benchmarks planning process, the Institute is expanding this program with increased focus on drugs to prevent the development of epilepsy and for treatment-resistant epilepsy.

• High throughput screening (HTS) rapidly tests large numbers of chemicals to find lead compounds for drug development and chemicals that are useful as research tools. Although the technology is widely used in industry, most neurological diseases are not sufficiently common to support commercial screening programs. The NINDS has awarded a contract for an HTS facility, and solicited proposals for the development of screening tests which can be adapted for high throughput screening. Ongoing screening efforts focus on ataxia telangiectasia, ALS, and Parkinson's disease.

• The NINDS is working closely with other components of NIH on the GPRA goal focused on the development of small molecules useful as tools or in drug development for neurological disorders, and is engaged in broad NIH Roadmap initiatives that will enhance many NIH drug development efforts, through better compound libraries, assays, databases, and other resources.

• The unique advantages of the NINDS intramural research program have been especially suited to fostering success in the translational arena. Enzyme and gene therapy for inherited metabolic disorders, new approaches to brain tumor treatment, and vaccine strategies for stroke prevention are among the avenues for therapy development that intramural scientists are pursuing.

Stem cells: NINDS intramural and extramural researchers have contributed to fundamental advances in understanding embryonic and adult stem cells; to improved methods for isolation, proliferation, and specialization of stem cells; and to promising therapeutic attempts in animal models of stroke, spinal cord injury, Parkinson's disease, demyelinating diseases, brain tumor, and several inherited metabolic disorders. The support of high quality research on all aspects of stem cell biology, from basic questions about what controls proliferation and specialization, to pragmatic concerns about what stage of specialization is appropriate for transplant therapies for various neurological disorders, is among the highest priorities of the Institute. An NINDS intramural researcher heads the new NIH facility which is characterizing the approved human

embryonic stem cell lines, and NINDS coordinates with other components of NIH through the NIH Stem Cell Task Force.

NINDS is planning initiatives in two critical areas of stem cell research. Understanding the *Interactions between Stem Cells and the Microenvironment* that they encounter in the brain is essential if stem cells are to be considered for therapeutic interventions in neurological disorders. Of particular interest is how interactions regulate stem cell survival, migration, replication and 'plasticity' in the nervous system under various conditions, such as with aging or following injury, disease or drug exposure. Fostering *Collaborative Research in Stem Cell Biology* is also a high priority so that methods for study of stem cells from one organ system can be applied to stem cells from other systems. The NINDS always encourages cooperation, but a targeted initiative will help investigators assemble interactive teams with the best expertise and resources to address significant questions in stem cell biology.

Genetics of Nervous System Disorders: Identification of defects in single genes that can cause disease has transformed neurology - improving diagnostic accuracy, providing insights about disease mechanisms, and allowing the development of cell culture and animal models that mimic human disorders for studying underlying disease processes and testing therapies. Gene findings have also demonstrated commonalities of mechanism that have energized research, both among different diseases and between the rare inherited and the more common type of diseases such as Parkinson's, ALS, and Alzheimer's.

Although studying single gene disorders continues to be a priority, it is interaction among multiple genes that confers susceptibility and influences progression of most common neurological disorders such as stroke, epilepsy, autism, Parkinson's disease, and multiple sclerosis. Understanding these complex genetic contributions is an emerging frontier in neuroscience. Following extensive discussions of complex genetics in disease-specific planning groups and workshops, the NINDS is placing increasing emphasis on complex genetics studies, which are expensive, but have a potentially high payoff. In FY 2005, the Institute will be expanding an initiative focused on complex genetics of neurological disorders.

Counterterrorism: Several chemical agents and toxins target the nervous system and could serve as terrorist weapons, and the nervous system is also vulnerable to infectious agents that could be used in a terrorist attack. The NINDS has consulted with the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) to identify high priority areas appropriate for NINDS to pursue, including persistent seizures, neuroprotection, and neurodegeneration. The greater diversity of the general public compared to the military in age, health status, and other respects is also an important issue for which NINDS has expertise that can complement the Army's programs. In FY 2003, NINDS initiated a program offering supplements to grantees to expand their research programs to issues relevant to counterterrorism, and posted a related website to help engage the neurological research community. Following a workshop in April 2004 to help the Institute develop a detailed plan for neurological research related to nerve agents, cyanide, and botulinum toxin, and to establish the groundwork for collaborations between DoD and NIH researchers, the Institute will expand the supplements program, and in FY 2005, solicit new grants and more targeted contract proposals, as appropriate.

Centers, collaborative efforts, and common resources: Because of the inherent multidisciplinary nature of basic and clinical neuroscience, team research and common resources are essential. The NINDS provides for this need generally through support for investigator initiated, multi-investigator grants and Center Core Grants (P30's), and specifically in programs such as the NINDS Cooperative Program in Translational Research, the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS), the Facilities of Research in Spinal Cord Injury, the high throughput screening center, microarray centers, the NINDS Human Genetics Repository, and centers focused on particular disorders, such as Parkinson's, autism, and muscular dystrophy. Enhancements of the NINDS efforts to foster collaborative research not discussed in the context of other initiatives include:

Parkinson's disease data coordination: The NINDS will solicit proposals for a Parkinson's Disease Data Organizing Center to support research on disease natural history, heterogeneity, diagnosis, and clinical-pathological correlations, and the identification of risk factors, neuroprotective factors or biomarkers. The center will coordinate data from the Morris K. Udall Centers of Excellence in Parkinson's Disease Research and other sources where longitudinal data are collected.

SPOTRIAS Network: The NINDS currently funds three Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS). The SPOTRIAS support clinical researchers from different specialties whose collective efforts aim to reduce the disability and mortality in stroke patients by translating basic research into rapid diagnosis and effective interventions. The program shows encouraging early signs of success, with candidate therapies already emerging. By FY 2005, NINDS anticipates the program will expand to a total of seven SPOTRIAS and a coordinating center to facilitate collective efforts among the centers.

Expanded patient-oriented research: Performance of patient-oriented research requires resources devoted to training personnel, ensuring appropriate inclusion and follow-up of subjects, monitoring patient safety, and coordinating activity among participating sites. In order to ensure that important patient-oriented projects proceed with adequate resources, NINDS is increasing the budget ceiling for clinical research in solicited centers, including SPOTRIAS, Udall Centers, and centers related to health disparities.

Muscular Dystrophy: The "Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001" (MD-CARE Act) authorized NIH to establish centers of excellence to conduct basic and clinical research in all forms of muscular dystrophy. The Muscular Dystrophy Cooperative Research Centers (MDCRCs) each bring together expertise, infrastructure and resources focused on major questions about muscular dystrophy, and together will be part of a national MDCRC Program focused on improving knowledge and treatment of muscular dystrophy. The NINDS, NIAMS, and NICHD collectively funded three of these centers in FY 2003, with the expectation that two more centers will be funded competitively in FY 2005.

Neurofibromatosis: Neurofibromatosis is the most common single-gene disorder affecting the nervous system. NF type 1 patients can develop benign peripheral nerve tumors (neurofibromas),

bone deformities, malignancies, vision loss, and learning disabilities. NF type 2 is characterized by tumors, particularly on or near the auditory nerve, which cause progressive hearing loss in one or both ears, tinnitus, and poor balance. Headache, facial pain, or facial numbness may also occur. For FY 2005, the NINDS will encourage the development of multidisciplinary research centers that capitalize on opportunities emerging from progress in understanding NF, and accelerate the development of therapies.

Health Disparities: The NINDS has made substantial investments to encourage minority scientists and to address health disparities in neurological disorders, through programs such as the Specialized Neuroscience Research Program (SNRP) and the Stroke Prevention/Intervention Program (SPIRP). Further investments are essential to maintain the progress, without losing a generation of diverse neuroscienctists, and to implement the NINDS Five-Year Strategic Plan on Minority Health Disparities, with its increased focus on diseases such as stroke, AIDS, and epilepsy. The NINDS is the NIH lead for the GPRA Goal to identify culturally appropriate, effective stroke prevention programs for nation-wide implementation in minority communities by FY 2010. The Institute supports many relevant clinical studies, clinical trials, and epidemiological investigations, but expanded activities will be necessary to accomplish this goal. Among activities planned for FY 2005, is the establishment of a stroke registry to guide the development of culturally appropriate stroke prevention and intervention research and quality of care improvement among Alaska Natives, in conjunction with the DHHS Indian Health Service.

Other Initiatives: The NINDS must respond to a wide range of mandates and to recommendations from planning groups, as well as to evident scientific opportunities and public health challenges within its mission. Major NINDS disease planning efforts include the Parkinson's Disease Research Agenda and Matrix; the Epilepsy Benchmarks; and the Brain Tumor and the Stroke Progress Review Groups (PRGs). The NINDS recently led the development of research goals for tuberous sclerosis complex (TSC) and reported on these to the U.S. Congress; the Muscular Dystrophy Coordinating Committee is developing the research and education plan for NIH required by the MD-Care Act; and the Interagency Autism Coordinating Committee is developing a research matrix for autism. In addition, the Institute remains cognizant of the recommendations of the IOM reports on multiple sclerosis and autism research issues. A few other examples of initiatives that respond to issues raised by planning efforts include:

Blood-Brain-Barrier and the Neurovascular Unit: The blood-brain barrier protects nerve cells from potentially harmful chemicals in the general circulation, but presents an obstacle for delivery of therapeutic agents to the brain. Understanding the blood-brain barrier in health and disease, and developing methods to deliver therapies across it, is critical for progress against many neurological disorders and will be a priority for FY 2005. A solicitation focused on neuroprotective barriers responds to needs identified as a high priority by the brain tumor, stroke, and Parkinson's planning efforts, as well as by workshops on inherited metabolic disorders. Similarly, a planned FY 2005 solicitation on the neurovascular unit responds to priorities in both the stroke and brain tumor PRGs.

Parkinson's Disease: The NINDS has initiatives in clinical trials, translational research, stem cells, centers, and genetics that relate directly to issues raised in the Parkinson's planning process. Other initiatives are planned in the areas of motor (dyskinesias) and non-motor (sleep,

depression) problems of Parkinson's. The NINDS will also work with NIEHS towards accomplishing the GPRA goal focused on improved animal models for Parkinson's disease.

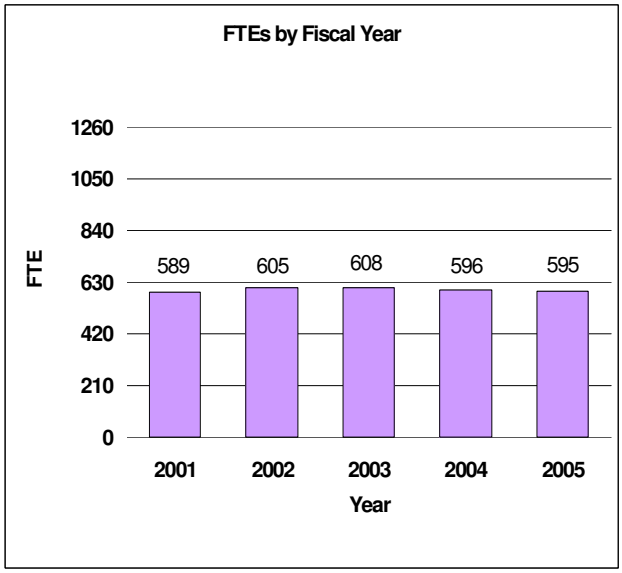
Pain: Pain is a major public health issue. The NINDS is developing solicitations focused on complex regional pain syndrome/reflex sympathetic dystrophy and on trigeminal nerve mediated pain disorders that follow up workshops relevant to these areas. Other program actions may emerge from the ongoing analysis of pain research by the re-energized NIH Pain Consortium.

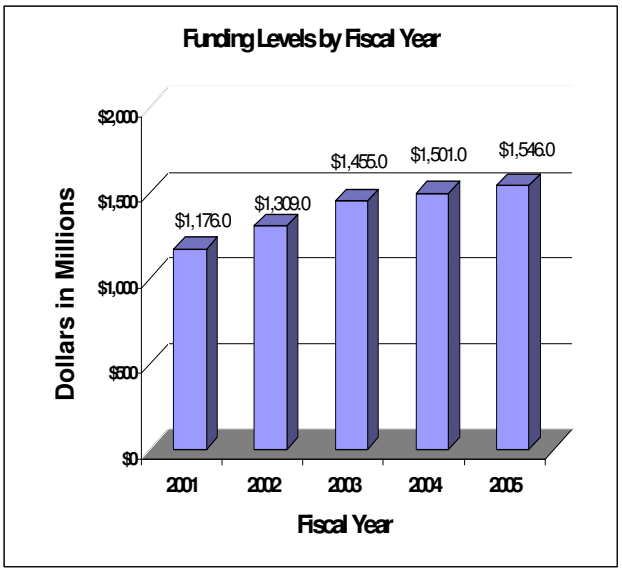
Scientific Workshops: The NINDS supports scientific workshops focused on specific diseases, cross-cutting research themes, emerging technologies, and specific clinical issues. Workshops assess the state of science, foster collaborations, attract scientists from other disciplines, and help the Institute determine how best to stimulate progress. Many workshops are held in cooperation with other components of NIH and with voluntary health organizations, as appropriate. Recent workshops, for example, have focused on diseases such as Batten disease, intracerebral hemorrhage, channelopathies, epilepsy, familial dysautonomia, HIV-dementia, human T-cell leukemia virus, metabolic disorders, multiple sclerosis, Parkinson's disease, spinal cord injury, and stroke; on technologies, such as brain imaging, deep brain stimulation, gene microarrays, and neural prostheses; on cross-cutting scientific areas, such as executive (cognitive) function, inflammation in chronic neurodegeneration, neurotrophic factors, and stem cells; and on broad issues, such as career development, clinical trials networks, and health disparities. Workshops under development focus on topics such as autism and epilepsy, pharmacotherapy in Parkinson's disease, the glycoproteinoses, biomarkers in multiple sclerosis, pediatric epilepsy models, anti-inflammatory strategies in stroke prevention, and rare immunologic disorders.

Budget Policy

The Fiscal Year 2005 budget request for the NINDS is $1,545,623,000 an increase of $44,930,000 and 3.0 percent over the FY 2004 Final Conference Level. Also included in the FY 2005 request, is NINDS's support for the trans-NIH Roadmap initiatives, estimated at 0.63% of the FY 2005 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NINDS are shown in the graphs below. Note that the Fiscal Year 2001 FTE figure is not comparable to the figures in the succeeding years due to NIH's consolidation of its Human Resources function in FY 2003.





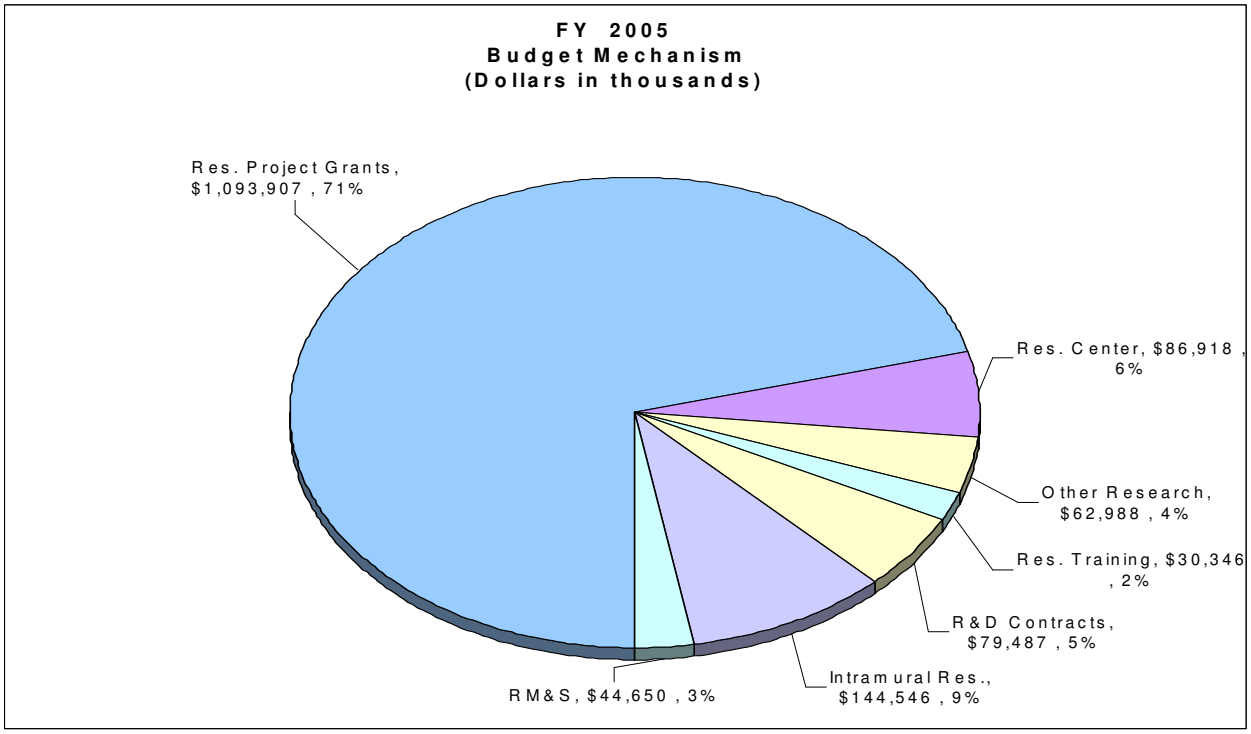
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The FY 2005 NIH request provides for an aggregate 1.3 percent increase in average cost for Research Project Grants, consistent with the Gross Domestic Product Deflator. The NINDS is providing an average cost increase of 1.9 percent for direct recurring costs in noncompeting continuation awards. Competing RPGs are based on an average cost increase of 1 percent.

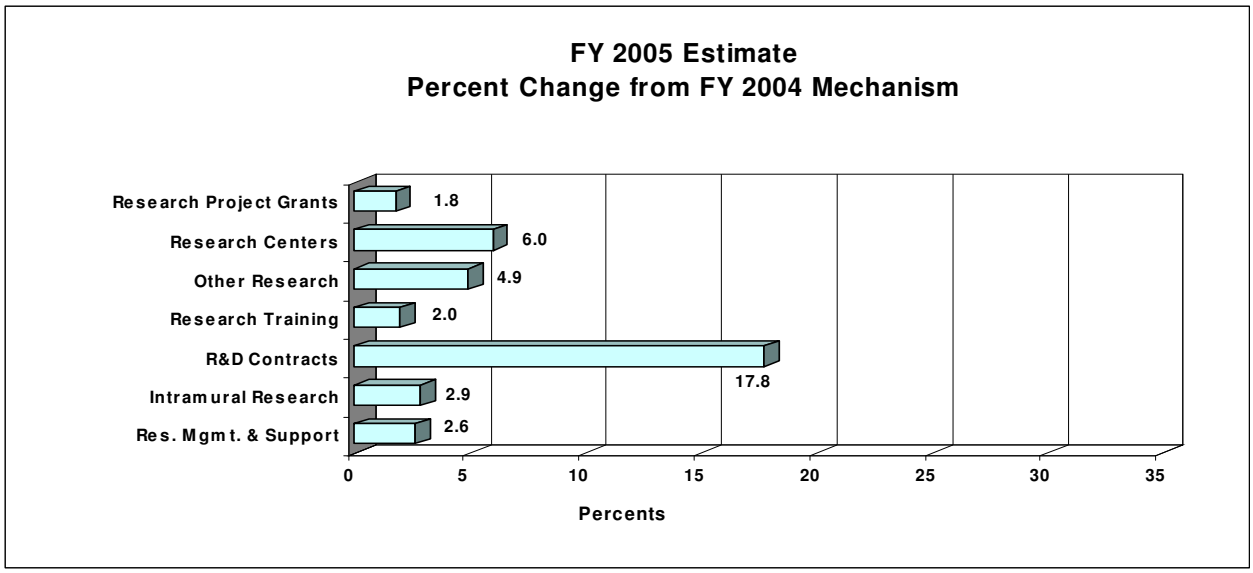
Advancement in medical research is dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2005 request, NINDS will support 749 pre- and postdoctoral trainees in full-time training positions. Stipend levels for pre-doctoral and post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will remain at FY 2004 levels.

The Fiscal Year 2005 request includes funding for 65 research centers, 364 other research grants, including 260 clinical career awards, and 150 R&D contracts. Intramural Research and Research Management and Support receive increases to support increased pay and estimated inflationary increases in FY 2005.

The NINDS will support the goals of the NIH obesity initiative through studies that contribute to a better understanding of the neurobiological basis of obesity. This budget includes $1 million for this initiative.

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





NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Mechanism - Total

MECHANISM	FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	1,991	$730,854,000	2,036	$812,951,000	1,890	750,308,000
Administrative supplements	(182)	8,688,000	(200)	12,008,000	(201)	12,219,000
Full funded	14	1,937,000	18	2,595,000	18	2,621,000
Single year	720	281,773,000	615	214,252,000	840	294,988,000
Subtotal, competing	734	283,710,000	633	216,847,000	858	297,609,000
Subtotal, RPGs	2,725	1,023,252,000	2,669	1,041,806,000	2,748	1,060,136,000
SBIR/STTR	124	32,623,000	128	35,588,000	130	36,552,000
Subtotal, RPGs	2,849	1,055,875,000	2,797	1,077,394,000	2,878	1,096,688,000
Research Centers:						
Specialized/comprehensive	61	69,903,000	64	81,356,000	65	85,938,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	1	644,000	1	980,000
Comparative medicine	0	405,000	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	61	70,308,000	65	82,000,000	66	86,918,000
Other Research:						
Research careers	214	32,013,000	244	36,440,000	260	38,935,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	42	7,190,000	47	7,800,000	47	7,800,000
Biomedical research support	0	982,000	0	1,029,000	0	1,036,000
Minority biomedical research support	6	1,799,000	10	3,065,000	10	3,105,000
Other	42	9,519,000	46	11,695,000	47	12,112,000
Subtotal, Other Research	304	51,503,000	347	60,029,000	364	62,988,000
Total Research Grants	3,214	1,177,686,000	3,209	1,219,423,000	3,308	1,246,594,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	312	11,772,000	322	11,960,000	322	11,960,000
Institutional awards	406	17,134,000	415	17,791,000	427	18,386,000
Total, Training	718	28,906,000	737	29,751,000	749	30,346,000
Research & development contracts	146	70,708,000	147	67,497,000	150	79,487,000
(SBIR/STTR)	(2)	(688,000)	(1)	(500,000)	(1)	500,000
	FTEs		FTEs		FTEs	
Intramural research	414	135,578,000	402	140,515,000	401	144,546,000
Research management and support	194	42,212,000	194	43,507,000	194	44,650,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Total, NINDS	608	1,455,090,000	596	1,500,693,000	595	1,545,623,000
(RoadMap Support)		(0)		(5,154,000)		(9,730,000)
(Clinical Trials)		(110,876,000)		(113,517,000)		(115,104,000)

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2003 Actual FTEs	FY 2003 Actual Amount	FY 2004 Final Conference FTEs	FY 2004 Final Conference Amount	FY 2005 Estimate FTEs	FY 2005 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Extramural Research		$1,277,300		$1,316,671		$1,356,427		$39,756
								0
		0		0		0		0
Subtotal, Extramural research		1,277,300		1,316,671		1,356,427		39,756
Intramural research	414	135,578	402	140,515	401	144,546	(1)	4,031
Res. management & support	194	42,212	194	43,507	194	44,650	0	1,143
Total	608	1,455,090	596	1,500,693	595	1,545,623	(1)	44,930

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Summary of Changes

FY 2004 Final Conference				$1,500,693,000
FY 2005 Estimated Budget Authority				1,545,623,000
Net change				44,930,000
	FY 2004 Budget Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$44,728,000		$672,000
b. Annualization of January 2004 pay increase		44,728,000		458,000
c. January 2005 pay increase		44,728,000		503,000
d. One less day of pay		44,728,000		(172,000)
e. Payment for centrally furnished services		22,449,000		673,000
f. Increased cost of laboratory supplies, materials, and other expenses		72,935,000		1,289,000
Subtotal				3,423,000
2. Research Management and Support:				
a. Within grade increase		19,723,000		344,000
b. Annualization of January 2004 pay increase		19,723,000		202,000
c. January 2005 pay increase		19,723,000		222,000
d. One less day of pay		19,723,000		(76,000)
e. Payment for centrally furnished services		7,239,000		217,000
f. Increased cost of laboratory supplies, materials, and other expenses		15,963,000		320,000
Subtotal				1,229,000
Subtotal, Built-in				4,652,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Summary of Changes--continued

CHANGES	FY 2004 Budget Base No.	FY 2004 Budget Base Amount	Change from Base No.	Change from Base Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,036	$824,959,000	(146)	($62,432,000)
b. Competing	633	216,847,000	225	80,762,000
c. SBIR/STTR	128	35,588,000	2	964,000
Total	2,797	1,077,394,000	81	19,294,000
2. Research centers	65	82,000,000	1	4,918,000
3. Other research	347	60,029,000	17	2,959,000
4. Research training	737	29,751,000	12	595,000
5. Research and development contracts	147	67,497,000	3	11,990,000
Subtotal, extramural				39,756,000
	FTEs		FTEs	
6. Intramural research	402	140,515,000	(1)	608,000
7. Research management and support	194	43,507,000	0	(86,000)
Subtotal, program		1,500,693,000		40,278,000
Total changes	596		(1)	44,930,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Budget Authority by Object

	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	596	595	(1)
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	$146,900	$151,420	$4,520
Average GM/GS grade	11.2	11.3	0.1
Average GM/GS salary	$70,640	$72,812	$2,172
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$75,325	$77,650	$2,325
Average salary of ungraded positions	114,084	117,592	3,508

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$28,255,000	$29,172,000	$917,000
11.3 Other than Full-Time Permanent	16,889,000	17,348,000	459,000
11.5 Other Personnel Compensation	1,143,000	1,179,000	36,000
11.7 Military Personnel	678,000	699,000	21,000
11.8 Special Personnel Services Payments	5,635,000	5,804,000	169,000
Total, Personnel Compensation	52,600,000	54,202,000	1,602,000
12.1 Civilian Personnel Benefits	11,349,000	11,694,000	345,000
12.2 Military Personnel Benefits	570,000	588,000	18,000
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	**64,519,000**	**66,484,000**	**1,965,000**
21.0 Travel & Transportation of Persons	2,973,000	3,046,000	73,000
22.0 Transportation of Things	1,553,000	254,000	(1,299,000)
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	84,000	86,000	2,000
23.3 Communications, Utilities & Miscellaneous Charges	926,000	949,000	23,000
24.0 Printing & Reproduction	520,000	532,000	12,000
25.1 Consulting Services	3,429,000	6,033,000	2,604,000
25.2 Other Services	10,248,000	10,631,000	383,000
25.3 Purchase of Goods & Services from Government Accounts	110,364,800	109,098,000	(1,266,800)
25.4 Operation & Maintenance of Facilities	1,128,000	1,588,000	460,000
25.5 Research & Development Contracts	22,626,000	35,856,000	13,230,000
25.6 Medical Care	255,000	261,000	6,000
25.7 Operation & Maintenance of Equipment	7,175,000	7,423,000	248,000
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**155,225,800**	**170,890,000**	**15,664,200**
26.0 Supplies & Materials	9,374,000	9,745,000	371,000
31.0 Equipment	16,342,200	16,695,000	352,800
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	1,249,174,000	1,276,940,000	27,766,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	2,000	2,000	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**1,436,174,000**	**1,479,139,000**	**42,965,000**
Total Budget Authority by Object	**1,500,693,000**	**1,545,623,000**	**44,930,000**

National Institute of Neurological Disorders and Stroke

Salaries and Expenses

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$28,255,000	$29,172,000	$917,000
Other Than Full-Time Permanent (11.3)	16,889,000	17,348,000	459,000
Other Personnel Compensation (11.5)	1,143,000	1,179,000	36,000
Military Personnel (11.7)	678,000	699,000	21,000
Special Personnel Services Payments (11.8)	5,635,000	5,804,000	169,000
Total Personnel Compensation (11.9)	**52,600,000**	**54,202,000**	**1,602,000**
Civilian Personnel Benefits (12.1)	11,349,000	11,694,000	345,000
Military Personnel Benefits (12.2)	570,000	588,000	18,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**64,519,000**	**66,484,000**	**1,965,000**
Travel (21.0)	2,973,000	3,046,000	73,000
Transportation of Things (22.0)	1,553,000	254,000	(1,299,000)
Rental Payments to Others (23.2)	84,000	86,000	2,000
Communications, Utilities and Miscellaneous Charges (23.3)	926,000	949,000	23,000
Printing and Reproduction (24.0)	520,000	532,000	12,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	927,000	950,000	23,000
Other Services (25.2)	10,248,000	10,631,000	383,000
Purchases from Govt. Accounts (25.3)	62,827,800	60,444,000	(2,383,800)
Operation & Maintenance of Facilities (25.4)	1,128,000	1,588,000	460,000
Operation & Maintenance of Equipment (25.7)	7,175,000	7,423,000	248,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**82,305,800**	**81,036,000**	**(1,269,800)**
Supplies and Materials (26.0)	9,354,000	9,725,000	371,000
Subtotal, Non-Pay Costs	97,715,800	95,628,000	(2,087,800)
Total, Administrative Costs	**162,234,800**	**162,112,000**	**(122,800)**

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

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

FY 2005 House Appropriations Committee Report Language (H. Rpt. 108-188)

Item
Epilepsy - Epilepsy remains a major, unsolved public health problem affecting the lives of millions of Americans and their families. The Committee seeks intensified efforts by the Institute in the prevention, treatment, and eventual cure of epilepsy. The Committee applauds the development of benchmarks for epilepsy research resulting from the "Curing Epilepsy: Focus on the Future" conference held in March, 2000. The Committee encourages NINDS to address the research issues related to the impact of seizures on young women, children, the elderly, and those with intractable or uncontrolled epilepsy. The Committee urges NINDS to develop specific research plans and goals for the anti-epileptic drug development program that has led to the discovery of many important anti-epileptic medications. (p 67)

Action taken or to be taken
The NINDS is committed to understanding the causes of epilepsy and developing effective therapies for all forms of epilepsy, with the ultimate goal of finding a cure. The Institute is actively engaged in addressing the 17 research benchmarks that will help epilepsy investigators maximize their research efforts towards the translation of basic science research findings into improved clinical therapies.

The NINDS currently supports a varied portfolio of epilepsy research projects, including many that have direct relevance to our understanding of seizure development in women, children, the elderly, and those individuals with intractable forms of the disease. For example, NINDS supports a number of studies on the relationship of hormonal fluctuations in females to epileptic changes in the brain, including one clinical trial examining whether adding the hormone progesterone to standard drug therapy will reduce seizure frequency in women with epilepsy.

The Institute is also funding a number of projects investigating the possible causes and mechanisms of seizure onset in the developing brain, the effects of early seizures on children's subsequent development (cognitive, emotional, language, and behavioral), and the risk of future development of intractable seizures in this population. A major new randomized, double-blind clinical trial is comparing the safety and efficacy of three widely-used antiepileptic drugs (AEDs) used in treating childhood absence epilepsy, with the aim of identifying the AED that provides the best seizure control with the fewest side effects. The researchers will also investigate genetic variations in drug metabolizing enzymes and other proteins that may influence a child's response to a particular AED, information that may aid in developing a genetic test to predict the optimal treatment for a given child. In March 2004, NINDS is co-sponsoring, with the University of California/Davis Health System, a conference to explore potential links between developmental seizure disorders and autistic disorders, which will foster discussion of possible neurobiological

connections, and provide a basis for future research. A workshop focused on the development of new animal models for pediatric forms of epilepsy is also being planned for the Spring of 2004.

The NINDS continues to support epidemiology studies of epilepsy in the elderly. For example, one study is focusing on the potential differences in the efficacy and side effects of antiepileptic medication in the elderly, while another is investigating the rate of status epilepticus, a particularly severe uncontrolled type of epilepsy that constitutes a medical emergency, in an elderly population. In addition, NINDS provided recently provided travel funds to allow both young researchers and minority researchers to attend an International Geriatric Epilepsy Symposium held in Miami, FL, in September 2003.

While all epilepsy research has the potential to improve the outlook for individuals with intractable epilepsy, NINDS supports a number of projects specifically addressing severe forms of the disease. These include a new study of the role that changes in the cellular structure of the brain might play in the development of intractable epilepsy, treatment studies of intractable epilepsy in children, a study of possible mechanisms underlying drug resistant forms of epilepsy, and studies of the mechanism of, and treatment for, status epilepticus. Of particular note is a multi-center, randomized clinical trial to determine whether early surgical treatment of mesial temporal lobe epilepsy (MTLE) is superior to continued medication management in reducing seizure frequency and improving quality of life.

The Anticonvulsant Screening Project (ASP), a component of the former program known as the Antiepileptic Drug Development Program, is a successful public/private translational effort supported by the NINDS for over two decades. During this time, the program has collected and screened approximately 25,000 compounds for specific anti-epileptic and central nervous system effects. As a result, approximately 23 drugs have been evaluated in clinical trials, with five ultimately being made available for widespread clinical use in treating epilepsy, as well as for other neurological disorders. This past year, two new compounds have advanced pre-clinically and will soon enter clinical investigations. Five other ASP-supported compounds are currently in various stages of clinical development. Over the past two years, the ASP, as part of the Epilepsy Benchmarks process, has sponsored two workshops on "Models for Epilepsy and Epileptogenesis" and "Identification and Validation of Epileptogenesis and Resistant Models Predictive of Human Efficacy," and has released a Request for Applications focused on validation of animal models for both seizure development (epileptogenesis) and highly resistant seizures. In addition, the ASP is developing a public database containing non-proprietary NINDS-generated data on certain classes of drugs that will assist the scientific community in new drug discovery efforts.

Item

Alzheimer's disease – Research supported by NINDS continues to play an integral role in widening the scientific base of knowledge about Alzheimer's disease. NINDS is working closely with the National Institute on Aging (NIA) in the area of immunotherapy for Alzheimer's disease, which can involve the production of antibodies that reduce the cellular and behavioral effects of the disease. The Committee encourages NINDS to continue to assign a high priority to its Alzheimer's research portfolio, and to continue to work closely with NIA and other institutes. (p. 67)

Action taken or to be taken

The NINDS continues to support critical research in Alzheimer's disease (AD), working closely with NIA and other NIH Institutes and Centers as appropriate. One of the emerging themes in the study of Alzheimer's disease and many other neurodegenerative diseases such as Parkinson's and Huntington's disease, is the overlap that researchers have been observing in the pathology underlying these conditions. Specifically, scientific reports are providing increasing levels of evidence that many of these disorders may be caused by similar abnormalities in protein folding and accumulation. As a result, every new finding in one of these diseases has the potential to impact the study of other neurodegenerative conditions, making NINDS support of AD research more relevant than ever. To explore these biological relationships, NINDS has joined NIA in supporting two meetings on this issue – one held in July 2001 and the second held in June 2003. Topics of the most recent meeting included the links between Parkinson's disease (PD) and AD-related genes and proteins in diverse neurodegenerative diseases and mechanisms for protein misfolding and accumulation.

In addition to jointly managing several grant awards on immunotherapy approaches to treating AD, NINDS also collaborated with NIA on its release of the grant solicitation on "Collaborative Studies on Alzheimer's Disease and Other Neurodegenerative Diseases Associated with Aging" in December 2002. The purpose of this Request for Applications was to facilitate collaborative cross-disciplinary and multi-institutional approaches that will contribute new and vital information about the clinical and pathological course of normal aging and the neurodegenerative diseases associated with aging. As a result of this solicitation, NINDS has funded a collaborative group of Alzheimer's Disease Centers that will investigate the differences between AD and "dementia with Lewy bodies," a degenerative disorder that is also related to PD at the clinical, pathological, and molecular levels.

Item

Amyotrophic lateral sclerosis (ALS) – ALS is one of a family of neurodegenerative diseases that plague millions of Americans. The Committee is pleased by the Institute's recent efforts to intensify its research into ALS, and commends NINDS on its multiple initiatives involving high throughput screening and assay development to identify compounds with activity in neurodegenerative disorders, including ALS. The Committee understands that the Institute has worked with voluntary associations as co-sponsors of some of these activities, and encourages NINDS to continue such productive partnerships to understand and develop treatments for ALS. These efforts may lead to possible prevention and treatment interventions for other degenerative disorders.

The Committee is also pleased by the January 2003 scientific workshop on ALS that NINDS held with the Department of Veteran Affairs (VA), as well as other entities. The Committee encourages the Institute's further collaboration with the VA in developing an initiative to address the scientific questions and gaps in the knowledge of ALS and motor neuron biology discussed at the workshop. The Committee also encourages the NINDS to coordinate, and collaborate on,

ALS research with other appropriate NIH Institutes, particularly the NIEHS, and continue its partnership with other organizations, as appropriate, to advance ALS research. (pp. 67-68)

Action taken or to be taken

The NINDS is fully committed to exploring all promising avenues of scientific research that could advance our understanding of ALS, and the Institute continues to partner with other NIH Institutes and Centers, as well as other Federal agencies and voluntary organizations on these activities whenever appropriate. To address the scientific questions and gaps in the knowledge of ALS and motor neuron biology discussed at the January 2003 workshop, NINDS joined the Department of Veterans Affairs and the Amyotrophic Lateral Sclerosis Association in releasing a Request for Applications in August 2003, on "The Etiology, Pathogenesis and Treatment of ALS." Some areas of focus for this RFA include the causes of disease across broad populations, including genetic and environmental causes, understanding the cellular interactions that contribute to the disease, the cellular and sub-cellular problems in affected tissues, novel approaches to delivery of therapies, and biomarkers for early disease detection.

Item

Transmissible spongiform encephalopathies (TSE) – The Committee recognizes the efforts of NINDS, in collaboration with NHLBI, to fund contracts for the development of a biological assay for TSE. The Committee requests that the Director of the Institute to be prepared to provide a report on the progress made toward the development of a TSE bioassay at the fiscal year 2005 appropriations hearing. The Committee is particularly interested in the success in detecting disease-causing agents in blood, saliva, cerebrospinal fluid, and other bodily fluids, as well as lymphoid tissue, especially tonsils (p.68).

Action taken or to be taken

The NINDS continues to support an extensive program of basic, applied, and clinical research on TSEs, including the contract program to develop tests to detect the presence of TSE agents in animal and human tissues. In the past year, building on decades of basic research implicating "prions" in human Creutzfeldt-Jakob disease, bovine spongiform encephalopathy (BSE or "mad cow disease") and chronic wasting disease (CWD) of deer and elk, scientists have developed a new approach to testing for prions using a very sensitive method called a "conformationally dependent immunoassay." The test shows promise for detecting prions not only from brain tissue after autopsy, but also from muscle tissue or blood from live animals. Although preliminary results are encouraging, extensive validation of this new testing method is essential and is underway.

Item

Therapies for multiple sclerosis and other immune system diseases—The Committee encourages NINDS and NIAID to continue collaborative efforts to investigate the role of neutralizing antibodies as described in the FY 2003 conference report. The Committee further encourages NIH to use all available mechanisms, including conducting a scientific workshop, to investigate the use of existing, approved pharmaceuticals, biologicals and other therapies as

platforms for combination therapies to address diseases of the immune system, such as multiple sclerosis, and other diseases. (p. 68)

Action taken or to be taken

Until new treatments are identified, combination therapy may be the best hope of improving treatment options for patients with relapsing MS. The NINDS recently issued the award for a large Phase III clinical trial on combination therapy in MS. The trial will involve 1000 subjects and be conducted at up to 40 clinical sites in the United States and Canada. The approved existing drugs to be tested are a form of interferon beta-1a (IFN-b) (Avonex®) in conjunction with glatiramer acetate (Copaxone®). In addition, this trial will investigate the role of neutralizing antibodies, and also provide an opportunity to examine the role of biomarkers in MS, as a tool for predicting clinical outcome and response to therapy.

The NINDS intramural program, housed at the Clinical Center on the NIH campus, has begun an open-label, Phase II trial evaluating the benefits of daclizumab (Zenapax®), which is an immunosuppressant that is FDA-approved to prevent acute organ rejection in renal transplants, but not for MS. The trial will examine the effect of daclizumab in relapsing-remitting MS patients, who have either failed, are not eligible for, or opted not to take standard therapies. The promising results from an earlier clinical study of daclizumab, in subjects who were taking interferon-beta, but responded incompletely, demonstrated that daclizumab is well-tolerated and inhibited inflammatory disease activity by almost 90 percent; this efficacy was maintained once interferon-beta therapy was discontinued.

In addition to these activities, the NINDS, in consultation with NIAID, will consider other mechanisms, including a workshop, that might be appropriate to address the issue of potential use of existing, approved pharmaceuticals and other agents, as combination therapies for MS, or other autoimmune disorders.

Item

Dystonia - The Committee continues to support the expansion of research on the neurological movement disorder dystonia, the third most common movement disorder. The Committee encourages NINDS to support additional research on both focal and generalized dystonia, and commends NINDS for its study of the DYT1 gene. The Committee encourages the Institute to continue its collaboration with the dystonia research community in supporting epidemiological studies on dystonia and in increasing public and professional awareness. The Committee commends NINDS for the recent release with other Institutes of the joint dystonia research program announcement. The Committee would like NINDS to be prepared to report on the dystonia research portfolio at the FY04 budget hearings. (p. 68)

Action taken or to be taken

The NINDS continues to support basic and clinical research into the causes and treatment of dystonia. The current dystonia portfolio includes studies of the genetic causes of dystonia, such as the DYT1 gene mutations; cellular effects of abnormal torsinA proteins; neuroimaging studies of basal ganglia function in dystonia; better characterization of clinical dystonic phenotypes; and

clinical trials of new treatments for dystonia. The NINDS also supports the "Taskforce on Childhood Motor Disorders," a group that recently published a consensus report that defines the clinical features of disorders like dystonia that cause hypertonia, or abnormally increased muscle tone, in children. This report will help to raise practitioners' awareness of dystonic syndromes. The Institute is also continuing its active intramural program of research on dystonia, including studies of underlying causes and early phase clinical trials of new treatment strategies.

In August 2002, the NINDS issued a program announcement in collaboration with the National Institute of Child Health and Human Development (NICHD), the National Institute for Deafness and Communicative Disorders (NIDCD), and the National Eye Institute (NEI) entitled "Studies into the Causes and Mechanisms of Dystonia"(PA-02-156). The announcement solicited applications for new studies on the underlying causes of human dystonia, secondary consequences of these movement disorders, and potential therapeutic strategies for treating these conditions. The Institute received an excellent response to the program announcement; the first set of applications submitted in response to the program announcement are currently undergoing peer review.

Item

Spina bifida – Spina bifida is the leading, permanently disabling birth defect in the U.S. The Committee urges NINDS to allocate resources to and prioritize research on primary and secondary prevention for spina bifida. (p.68)

Action taken or to be taken

Neural tube defects (NTDs) are serious birth defects that involve incomplete development of the brain, the spinal cord or their protective coverings. Spina bifida, the most common neural tube defect, results when a part of the developing neural tube fails to close. The NINDS currently funds grants to identify and understand the risk factors for neural tube defects, including spina bifida. NINDS-funded researchers are working to identify the genetic factors involved in the development of neural tube defects. In one project, researchers are testing the hypothesis that certain genetic factors may diminish the availability of folate to the fetus, thereby contributing to spina bifida. The ultimate goal of this research is to understand how folate supplements prevent spina bifida, so that folate supplements for pregnant women can be made more effective. In addition, other NINDS-funded researchers are assessing environmental risk factors to help uncover potential gene/environment interactions.

The NINDS also funds a wide range of basic research that may help to decipher the mechanisms underlying the development of spina bifida, and to devise strategies for preventing or treating the disorder. Since spina bifida results from the failure of the spine to close properly during the first month of pregnancy, understanding at the molecular level of how complex structures such as the brain and spinal cord are constructed will offer clues to understanding what goes awry in birth defects like spina bifida. The NINDS supports research on the genes that are expressed in and around the nascent neural tube, and how these genes instruct cells of the nascent neural tube to assume particular positions and fates. Scientists funded by NINDS are also studying the signals that are responsible for the induction, migration, and differentiation of a specialized subset of

cells, known as the neural crest, which emerge from the neural tube as it is in the process of closing, and which give rise to a range of cell types, including those that form most of the peripheral nervous system.

The Third International Conference on Neural Tube Defects was held September 27-30, 2003, in South Carolina. This conference was supported by NINDS, NICHD, NIDCR, and the March of Dimes/South Carolina. This conference brought together researchers from various disciplines to discuss recent advances in basic and clinical research and to establish new collaborations for future research that includes sharing of biological samples. The speakers were world-recognized for their contributions to understanding the pathogenesis, molecular biology, and epidemiology of neural tube defects. Since the conference, the principal investigator and conference organizer have worked with program staff to organize banking of blood/DNA samples in an NIH repository, which will allow sharing of these rare and important biological patient samples.

Item

Tuberous sclerosis – Tuberous sclerosis complex (TSC) is a genetic disorder that affects many different organ systems. Genetic links provided by the TSC genes and research on TSC provide significant implications for scientific advancement benefitting other large patient populations suffering from epilepsy, lung disease, cancer, diabetes, autism, learning disabilities, and mental retardation. The Committee encourages NINDS to enhance research in this area, including consideration of the development of a comprehensive TSC patient registry, epidemiology studies on the natural history of TSC, and animal models/cell lines (p. 69)

Action taken or to be taken

In July 2003, the NIH released a strategic research plan for TSC, spearheaded by NINDS, which defined the following long-term goals: determine the molecular and cellular basis of TSC; understand and treat the symptoms of TSC; understand the expression of TSC symptoms across the life span and identify factors that affect this expression, such as natural history studies; develop resources that accelerate TSC research, including a general clinical database of TSC patient information and new animal/cell line models; and create new research opportunities. While this strategic plan is intended for the entire TSC research community, the NINDS is already helping to implement many of the specific objectives. Several NINDS-supported studies are underway to investigate the relationship between mutations in the TSC genes and the development of neurological abnormalities. For example, NINDS-funded researchers are generating mice with TSC2 mutations expressed in specific organs to explore the pathogenesis of TSC in the brain, heart, and kidney, and using a rat model of TSC2 to explore the relationships between TSC gene mutations, central nervous system tumors, and seizures. Researchers are also employing genetic and biochemical strategies to identify new components of the molecular pathway through which the TSC genes control cell growth and proliferation, including a newly awarded grant that employs mouse models. In addition, NINDS-supported projects are underway to examine tryptophan metabolism as a potential marker for epilepsy and autism in TSC patients, and to develop gene therapy strategies to control tumor growth in animal models of TSC. The NINDS continues to reassess research needs and implementation strategies by sponsoring periodic meetings on TSC; this past year, NINDS sponsored a symposium on TSC at the annual

Child Neurology Society meeting. The Institute has also launched a new translational research program of cooperative agreements that will support milestone-driven projects focused on the identification and preclinical testing of new therapeutics for neurological disorders. One such recently awarded project will directly address whether rapamycin has the potential to treat TSC, and will collect critical preclinical data to support the therapeutic use of rapamycin in TSC. This work is a prerequisite to undertaking clinical trials in people.

Item

Juvenile diabetes – The Committee commends NINDS for its efforts to prevent and treat hypoglycemia and neuropathy, both of which are serious complications of diabetes and demonstrate accelerated development in individuals with juvenile diabetes. The Committee encourages NINDS to expand its research in neuropathy by considering the establishment of centers specifically for detection and prevention of this dangerous complication of diabetes. (p.69)

Action taken or to be taken

The NINDS has recently increased its efforts to combat the neurological complications of type 1 diabetes, also known as "juvenile diabetes," since it often develops in children and young adults, although the disorder may appear at any age. In FY 2003, NINDS co-sponsored, along with other NIH Institutes and Centers, four requests for applications (RFAs) aimed at understanding and treating type1 diabetes and its complications. These initiatives are designed to attract new research talent to type1 diabetes research, and facilitate the formation of interdisciplinary research partnerships; to improve understanding of hypoglycemia, including the effects on brain function, and to enhance treatment strategies for hypoglycemia in patients with diabetes; to encourage translation of findings on the molecular basis of type1 diabetes into new therapies for the prevention, treatment, and cure of this disease; and to encourage the use of recent developments in proteomics and metabolomics technologies to study type1 diabetes and its complications. These FY2003 initiatives expand NINDS research on the neurological complications of diabetes, including diabetic neuropathy and the effects of hypoglycemia on brain function, that was further stimulated by earlier RFAs in FY 2000 and FY 2001. The NINDS also funds a wide range of basic research on understanding and treating neuropathy, including HIV/AIDS-related neuropathy and hereditary neuropathies, such as Charcot-Marie-Tooth disorder.

Research centers are only one of the many ways that NIH can support research. The many initiatives in the area of type1 diabetes in which NINDS has participated in the past few years have been more appropriate, and highly successful, means to encourage a wide range of research into this disorder and its complications, including diabetic neuropathy. The NINDS will continue to utilize all available mechanisms, as appropriate, to continue and expand its research in this area.

Item

Neurofibromatosis (NF)– Advances in NF research have linked NF to cancer, brain tumors, learning disabilities and heart disease affecting over 150 million Americans. Because NF

regulates both the RAS and cAMP pathways relating to cell growth and cognition, NF plays a pivotal role both in disorders of the brain and in cancer. The enormous promise of NF research is now reaching fruition in the testing of potential therapies. Therefore, the Committee encourages NINDS to enhance its NF clinical and basic research portfolios through clinical trials, RFAs, and other funding mechanisms to accelerate and exploit the substantial progress in NF research. The Committee commends NINDS for its leadership role in NF research and in coordinating efforts with other Institutes engaged in NF research (p. 69)

Action taken or to be taken

The NINDS continues to support a balanced portfolio of investigator-initiated research on NF, including studies on the molecular pathways through which the NF1 and NF2 gene products control cell proliferation and migration, the mechanism by which particular types of tumors form in NF1 and NF2, and the correlation between mutations and symptoms in NF patients. The results of these studies may aid in the development of a rapid molecular diagnostic test for NF and effective management of the disorder. To encourage the translation of this basic research into potential therapies, NINDS recently issued a program announcement (PAR-04-018) to solicit applications for "National Centers for Neurofibromatosis Research;" each center must propose three projects, at least one of which must be translational or clinical in nature.

The NINDS has also supported several NF conferences. The Institute and the NIH Office of Rare Diseases (ORD) cosponsored a December 2003 workshop, "Accelerating Therapy Development for Neurofibromatosis," which identified roadblocks to drug development and suggested strategies for eliminating them. The participants were drawn from academia, drug companies, patient voluntary organizations, NIH, the Department of Defense, and the U. S. Food and Drug Administration. The NINDS also continues to competitively provide funding for the annual meetings of the NNFF International Consortium for the Molecular Biology of NF1 and NF2, which have been held for more than a decade and have spawned key collaborations in NF research.

Item

Reflex sympathetic dystrophy syndrome (RSD) – The Committee recognizes the substantial burden RSD imposes upon people and the lack of understanding and adequate treatment for this disease. The Committee commends the NINDS for holding the December, 2001 state of the science meeting on RSD and encourages NINDS to follow through on the meeting's recommendations, including efforts to develop standardized diagnostic criteria, to assess risk factors and incidence through epidemiology studies, to develop and validate animal models and **to explore avenues for developing treatments.** (p. 69)

Action taken or to be taken

The NINDS and the Office of Rare Diseases at NIH sponsored a meeting in December 2001 entitled "Reflex Sympathetic Dystrophy/Complex Regional Pain Syndrome: State-of-the-Science," to discuss the state-of-the-science in RSD, also known as Complex Regional Pain Syndrome type I (CRPS), and to identify new directions for research on this chronic debilitating condition. The consensus among the participants at the meeting was that an interdisciplinary and

multidisciplinary research approach was needed to better understand the underlying mechanisms of RSD/CRPS and improve treatment of patients with this disorder.

In May 2003, NINDS issued a program announcement (PAS-03-120) with one million dollars in set-aside funds to encourage research into many of the areas that were recommended at the conference. This PAS is intended to encourage scientists from various disciplines to engage in research focused on a mechanism-based diagnostic classification of RSD/CRPS patients, which might lead to a mechanism-based therapeutic strategy for this chronic condition. The development of standardized diagnostic criteria, assessment of risk factors and incidence through epidemiology studies, development and validation of animal models, and development of new treatments are included in the list of potential research areas that would be responsive to the goals of this initiative.

Item
Lupus-Individuals with lupus commonly experience headaches, confusion, difficulty concentrating, and occasionally seizures, strokes, or other disorders of the nervous system. Stroke and seizures are a serious health effect of lupus. The Committee encourages NINDS to enhance efforts to study the neurological aspects of lupus. (p. 70)

Action takes or to be taken
Systemic lupus erythematosus (SLE) is a systemic inflammatory autoimmune disease that affects predominantly young, minority women. Up to 75 percent of patients experience some type of nervous system manifestations during their disease course, one of the most serious being stroke.

The NINDS supports investigators who are studying the presence and variations of a particular antibody that promotes blood clotting in lupus patients to ascertain what role it plays in their elevated stroke risk. Other factors that might promote stroke and cognitive dysfunction in these patients are also being closely examined. It is anticipated that these studies will provide important information about the relative importance of genetic factors on vascular disease risk in SLE, and pave the way for tests to predict neurological manifestations in lupus patients. A very successful study giving strong evidence of cognitive problems in patients with lupus was recently completed. The NINDS is encouraging investigators to follow up on these findings.

The NINDS is planning a 2004 scientific workshop on "Anti-Inflammatory Strategies in Stroke," which will include a discussion of autoimmune mechanisms in the development of cerebrovascular disease. Although the workshop will not focus specifically on SLE, it should further understanding of the immune-cerebrovascular interactions observed in SLE.

Item
Down syndrome – Down syndrome is caused by extra genetic material on the 21st chromosome. It is the leading genetic cause of mental retardation in humans. The Committee encourages NINDS to enhance its efforts on Down syndrome, particularly as it relates to cognitive enhancement. (p.70)

Action taken or to be taken
As the most frequent cause of mild to moderate mental retardation, the NINDS is actively engaged in supporting research to address Down syndrome. The Institute funds research focused on understanding the neuroanatomical and physiological abnormalities in Down syndrome, the genetic and molecular basis for the degeneration of specific neuronal populations in the brains of elderly Down syndrome patients, and the role of different genes in various aspects of Down syndrome. In the last four years, NINDS funding for Down syndrome research has more than doubled.

In addition to the research it supports, NINDS was one of the sponsors of the "10th International Meeting on the Molecular Biology of Chromosome 21 and Down Syndrome," held in September 2002 in Spain. Presentations at this meeting included research on a genetic analysis of chromosome 21; downstream targets of genes and the molecular pathways involved in the disorder; neuropsychology of Down syndrome; research using mouse models of the disorder; and future directions in research.

The NINDS will continue to support and enhance its Down syndrome research, including relevant aspects of cognitive enhancement, and will coordinate its efforts with other NIH institutes to help advance research on Down syndrome and other related disorders.

Item
Mucolipidosis type IV (ML4) – Building on the identification of the gene that causes this debilitating genetic metabolic disorder, the Committee encourages NINDS to expand its efforts to support research leading to possible treatments and cures for those with ML4. In particular, NINDS is encouraged to support research involving other organisms which bear genes resembling the one whose mutation in humans causes ML4. This research should also offer insight into other genetic disorders (p. 70)

Action taken or to be taken
Researchers supported by NINDS were among those who discovered that defects in the MCOLN1 gene are responsible for ML4, and NINDS continues to support research on how the mutations contribute to the ML4 pathophysiology. New NINDS-funded projects include the generation and characterization of a mouse model of ML4, and a screen for genes that may serve as potential drug targets for ML4. In addition to funding research specifically focused on ML4, NINDS also supports research on other lysosomal storage disorders, as well as gene therapy and pediatric neuroimaging research, all of which may ultimately speed progress toward finding treatments for ML4.

Item
Mucopolysaccharidosis (MPS)– The Committee is encouraged by NINDS sponsorship of a scientific conference focusing on central nervous system issues and the barriers to and development of effective therapies for MPS disorders. The Committee urges NINDS to solicit and provide for investigator proposals resulting from the findings of this conference. The Committee encourages NINDS, in collaboration with NIDDK and NICHD, to support current

MPS research and study of the blood brain barrier as an impediment to treatment, and to use all available mechanisms to further stimulate and enhance efforts to better understand and treat MPS disorders. (p. 70)

Action taken or to be taken

The mucopolysaccharidoses are a group of inherited lysosomal storage disorders. The NINDS, NIDDK, NICHD, the Office of Rare Diseases (ORD), and the National MPS Society co-sponsored the workshop, "The Mucopolysaccharidoses: Therapeutic Strategies for the Central Nervous System," held in September 2002 to identify relevant scientific issues and future research priorities. The participating Institutes are pursuing the recommendations of the meeting in accordance with their individual research missions. For example, the NIDDK's "Molecular Therapy Core Centers" support gene and other molecular therapy research on genetic diseases; two of the four Centers study MPS. These Centers are a resource that can be used by investigators working on MPS, who are supported by various Institutes. The NINDS currently funds several projects aimed at developing gene therapy strategies to prevent and reverse the effects of MPS. In addition, NINDS funds basic and cross-cutting research in stem cell biology and pediatric neuroimaging that will be crucial for progress against MPS, as well for many other diseases.

In FY2003, the NINDS issued a program announcement with set-aside funding (PAS-03-165), "Neuroprotective CNS Barriers in Neurological Diseases," to solicit research on the biology of the blood-brain barrier, and on strategies to deliver therapeutic agents, including gene therapy vectors, across it. This initiative is directly responsive to the research priorities identified at the September 2002 workshop, and addresses a major obstacle impeding the development of effective therapies for MPS disorders. In addition, the NINDS will be sponsoring an international workshop in Spring 2004 on advances in the pathogenesis and therapy of the glycoproteinoses, another group of lysosomal storage disorders. This meeting, which will include presentations on aspects of MPS research, is designed to facilitate data and resource sharing, including animal models; to foster research collaborations; and to discuss various means to advance basic and translational research in this area. The NINDS also plans to issue a program announcement, with set-aside funding, in FY2005 to stimulate research on therapy development for lysosomal storage diseases.

FY 2005 Senate Appropriations Committee Report Language (S. Rpt. 108-81)

Item

Alzheimer's Disease – Research supported by NINDS continues to play an integral role in widening the scientific base of knowledge about Alzheimer's disease. NINDS is working closely with NIA in the area of immunotherapy for Alzheimer's disease, which can involve the production of antibodies that reduce the cellular and behavioral effects of the disease. The Committee encourages NINDS to continue to assign a high priority to its Alzheimer's research portfolio, and to continue to work closely with NIA and other institutes. The Committee urges the NINDS, in collaboration with the NIA and NIMH, to expand its research into early diagnosis

of Alzheimer's using PET imaging of the brain, and to share its results with the Centers for Medicare and Medicaid Services. (p. 121)

Action taken or to be taken

The NINDS continues to support critical research in Alzheimer's disease (AD), working closely with NIA and other NIH Institutes and Centers as appropriate. One of the emerging themes in the study of Alzheimer's disease and many other neurodegenerative diseases such as Parkinson's and Huntington's disease, is the overlap that researchers have been observing in the pathology underlying these conditions. Specifically, scientific reports are providing increasing levels of evidence that many of these disorders may be caused by similar abnormalities in protein folding and accumulation. As a result, every new finding in one of these diseases has the potential to impact the study of other neurodegenerative conditions, making NINDS support of AD research more relevant than ever. To explore these biological relationships, NINDS has joined NIA in supporting two meetings on this issue – one held in July 2001 and the second held in June 2003. Topics of the most recent meeting included the links between Parkinson's disease (PD) and AD-related genes and proteins in diverse neurodegenerative diseases and mechanisms for protein misfolding and accumulation.

In addition to jointly managing several grant awards on immunotherapy approaches to treating AD, NINDS also collaborated with NIA on its release of the grant solicitation on "Collaborative Studies on Alzheimer's Disease and Other Neurodegenerative Diseases Associated with Aging" in December 2002. The purpose of this Request for Applications was to facilitate collaborative cross-disciplinary and multi-institutional approaches that will contribute new and vital information about the clinical and pathological course of normal aging and the neurodegenerative diseases associated with aging. As a result of this solicitation, NINDS has funded a collaborative group of Alzheimer's Disease Centers that will investigate the differences between AD and "dementia with Lewy bodies," a degenerative disorder that is also related to PD at the clinical, pathological, and molecular levels.

The NINDS continues to support imaging studies that might provide earlier diagnosis of AD, and potentially permit earlier intervention. The NINDS has recently awarded a grant to support the use of PET imaging to examine plaques and tangles, the cellular hallmarks of AD, in individuals with a genetic predisposition to the disorder. The plaques and tangles will be labeled with a molecular "tag," and regions that are imaged with this tag will be superimposed onto functional magnetic resonance images (fMRIs) taken while a person performs a memory task. The overlap between the two images should enable researchers to link AD-related changes at the cellular level to regions of the brain that may be selectively activated during memory tasks. Other studies are also exploring the use of MRI to examine how brain activation patterns change over time in individuals at high risk for AD, and in a separate study, to determine if the degeneration of specific brain regions may be a hallmark of pre-clinical AD. It is anticipated that the investigators conducting these imaging studies will publish their findings in peer-reviewed medical journals, which would make the data publicly available and accessible to the Centers for Medicare and Medicaid Services.

In addition to these specific awards, NINDS has also collaborated with NIA and a number of other NIH Institutes on a workshop in 2001 and a Program Announcement, released in April 2003, that encourages applications on the "Development and Application of PET and SPECT Ligands for Brain Imaging Studies." Although broad in its scope, imaging tools that could be useful for studying AD would be appropriate for development under this solicitation.

Item

Amyotrophic Lateral Sclerosis [ALS]- ALS, or "Lou Gehrig's disease," is one of a family of neurodegenerative diseases that plague millions of Americans. The Committee is pleased by the Institute's recent efforts to intensify its research into ALS, and it commends NINDS on its multiple initiatives involving high-throughput screening and assay development to identify compounds with activity in neurodegenerative orders, including ALS. The Committee understands that The ALS Association has been involved as a co-sponsor in some of these activities, and urges the Institute to continue such productive partnerships in its efforts to understand and develop treatments for ALS, which can lead to possible prevention and treatment interventions for other degenerative disorders. (p. 121)

Action taken or to be taken

The NINDS is working closely with the ALS Association toward our common goal of translating the increased understanding about ALS into treatments that help people with this terrible disease. The ALS Association was directly involved in the NINDS Drug Screening Consortium, which brought together investigators from 26 institutions to screen a set of 1040 chemical compounds in assays (simple laboratory tests) for activity against neurodegenerative diseases, including ALS. The NINDS and the ALS Association together are supporting the next step from that project--testing the best candidates from that screening in more rigorous animal models of ALS. At the new NINDS high throughput screening facility, three of the first assays undergoing evaluation for testing are focused on ALS. More broadly, the Institute's continuing efforts, through the NIH Roadmap process and other avenues, in the area of chemical libraries, databases for drug discovery, technology development, and screening facilities may also benefit neurodegenerative diseases, including ALS, as will the comprehensive translational research program that the NINDS has successfully launched.

Item

ALS collaboration with Department of Veterans Affairs – . . . .The Committee is also pleased by the January 2003 scientific workshop on ALS that the NINDS held with the Department of Veterans Affairs [VA]. The Committee encourages the Institute's further collaboration with the VA in developing an initiative to address the scientific questions and gaps in the knowledge of ALS and motor neuron biology discussed at the workshop. The Committee also encourages the NINDS to coordinate and collaborate on ALS research with other appropriate NIH Institutes, particularly the NIEHS, and to continue its partnership with other organizations, as appropriate, to advance ALS research. (p. 121)

Action taken or to be taken
Please refer to page NINDS - 31 of this document for NINDS response to this item regarding ALS collaboration with Department of Veterans Affairs.

Item
Ataxia Telangiectasia [A-T]– A-T is a genetic disease that attacks in early childhood. It progressively affects coordination and severely compromises the immune system. Children with A-T are highly likely to develop cancer, and rarely live beyond their teens. The Committee encourages the NINDS to work with the NCI and other appropriate Institutes to support research aimed at understanding the underlying causes of A-T with the goal of translating this basic research into treatments for the disease (p. 122)

Action taken or to be taken
The NIH helped support the discovery of the Ataxia Telangiectasia Mutated (ATM) gene defect that causes A-T, and continues to fund research aimed at understanding the normal functions of the ATM gene and how defects cause disease. The National Cancer Institute (NCI) supports studies to identify the role of ATM mutations in the development of cancer, which presents a compelling example of how research on a rare disease can have much broader implications. The NIGMS also funds several studies on the mechanism of action of ATM in normal cells. In addition to supporting basic research to understand how A-T affects on the brain, the NINDS is using what we have learned so far in trying to develop therapies, including the development of new animal models in which to test potential treatments; conducting screens for chemicals that counteract the effects of ATM mutations; and doing preclinical testing of potential drugs. In January 2003, the Institute held a workshop focused specifically on selecting an A-T assay–that is, a simple laboratory test–that could be used for large scale drug screening; one of the first projects now underway at the new NINDS high throughput screening facility is screening for potential leads to develop drugs for A-T.

Item
Batten Disease- The Committee is once again disappointed with the pace of research regarding Batten disease. The Committee strongly urges the Institute to increase funding for such research by actively soliciting grant applications for Batten disease and taking aggressive steps to assure that a vigorous research program is established. The Committee requests the Institute to inform the Committee of the steps taken to increase research on Batten disease (p. 122)

Action taken or to be taken
The NINDS supports a vibrant and multi-faceted research portfolio on Batten disease, which generally refers to a group of disorders known as Neuronal Ceroid Lipofucinoses, including studies of the molecular pathway underlying the disease, the effects of the disease at the cellular and subcellular levels, the development of animal models, and preclinical testing of potential therapies. An NINDS researcher recently reported a significant finding that suggests that individuals with juvenile Batten disease may mount an autoimmune response to an enzyme that normally converts an excitatory neurotransmitter to an inhibitory one. The resulting excess excitatory neurotransmitter could contribute to the seizures and other symptoms observed in

Batten patients. The NINDS has awarded a new grant to follow up on this discovery, and also held a workshop in November 2003 to further explore this finding. In addition, the NINDS, in conjunction with the Office of Rare Diseases and the National Institute of Child Health and Human Development (NICHD) sponsored the "9th International Conference on Neuronal Ceroid Lipofucinoses" in April 2003. This conference provided a forum for Batten researchers from around the world to present their work on Batten genes and gene products, establish collaborations, and explore ways to translate advances at the basic research level into clinical applications. The NINDS research programs in stem cell biology, gene therapy, pediatric neuroimaging, and drug screening for neurodegenerative disorders, while not directed specifically at Batten, are also likely to speed progress toward finding treatments for this disease.

Item

Brain Tumors- The Committee continues to be concerned that not enough attention is being given by NINDS to identifying causes of and treatments for brain tumors and encourages NINDS to continue working with NCI to carry out the recommendations of the Report of the Brain Tumor Progress Review Group (p. 122)

Action taken or to be taken

Brain tumor research is a priority of the NINDS, and the Institute has recently initiated activities to address the recommendations in the Report of the Brain Tumor Progress Review Group (BT-PRG). In March 2003, NINDS issued a Program Announcement with set-aside funding (PAS) to promote discovery of susceptibility genes for complex neurological disorders, including brain tumors. More recently, NINDS issued a PAS to stimulate research on the blood-brain barrier—deemed an especially high priority by the BT-PRG. In FY 2005, NINDS plans to issue a program announcement to solicit grant applications aimed at understanding and preventing brain tumor migration, which is specifically responsive to the research priority on understanding the biology of brain tumors.

Many ongoing, investigator-initiated projects also address recommendations of the BT-PRG. NINDS-funded investigators are conducting research on the molecular pathways underlying tumor formation and tumor cell invasion; preclinical studies aimed at developing new approaches to chemotherapy, radiation therapy, and gene therapy; clinical trials to test the safety and efficacy of these new approaches; and the development of new neuroimaging tools and animal models for brain tumor research and diagnosis.

The NINDS continues to work closely with NCI to promote and strengthen the brain tumor research enterprise. Program directors from the two institutes have formed a Brain Tumor Working Group that meets regularly to review their brain tumor research portfolios, monitor progress, identify research needs, and address issues related to implementation of the recommendations of the BT-PRG. NINDS and NCI staff have also joined forces on specific projects, such as the Brain Tumor Genome Anatomy Project (BTGAP). The BTGAP, which was designed to develop a comprehensive molecular profile of primary brain tumors at progressive levels of malignancy, is nearing completion of the data collection phase, and beginning to explore strategies for data analysis. The NINDS and NCI jointly support a Specialized Program

of Research Excellence (SPORE) on brain tumors, which focuses on identifying new potential therapeutic agents, overcoming chemotherapy resistance, and identifying environmental risk factors for human gliomas, which constitute approximately half of all primary brain tumors and are particularly lethal.

Item

Cognitive Neuroscience - By encouraging research on higher brain functions that underlie complex behaviors such as learning, memory, attention, and cognition, the NINDS will continue to unlock secrets not only on basic brain structure and function, but also on neural activity **associated with specific cognitive processes. The Committee is interested in seeing progress in this research.** (p.122)

Action taken or to be taken

A major portion of the NINDS behavioral and social science research portfolio consists of research aimed at understanding the neural bases of a variety of cognitive and behavioral processes. The NINDS has also sponsored a number of recent workshops and initiatives, which demonstrate the NINDS commitment to these areas.

In January 2003, a number of Institutes and Centers at NIH, including NINDS, initiated the "Mind-Body Interactions and Health: Exploratory/Developmental Research Program" for infrastructure grants in support of research on the relationships among cognition, emotions, personality, social relationships, and health. In June 2003, NINDS, together with other NIH Institutes, sponsored a workshop on "Executive Function: Current Knowledge and Future Research Opportunities" to bring together leaders in the field to discuss current research findings in executive function, assess the state of knowledge regarding executive function in the healthy and injured/diseased states, and set a research agenda for future studies of executive function. The NINDS and other NIH institutes are developing an initiative that will address the critical need for a battery of tests of executive function, which includes higher level cognitive processes such as working memory, decision-making, anticipation, and planning, that will be adaptable to clinical trials relevant to each Institute's mission.

In September 2003, NINDS, together with NIMH, the National Science Foundation (NSF) and Princeton University, sponsored the workshop, "About Faces: A Multidisciplinary Approach to the Science of Face Perception." Face perception plays a central role in social communication. Disorders, such as autism, Asperger's syndrome, stroke, schizophrenia, depression, Parkinson's disease, Alzheimers' disease and social phobia, are associated with impaired social communication. The goal of the workshop was to develop better models of the cognitive processes and neural systems underlying face perception in order to provide better probes for investigating the pathophysiology of these disorders, and possibly, better outcome measures for treatment trials. This year, NINDS will hold a meeting on "Cognitive Rehabilitation Interventions: Moving from Bench to Bedside," to explore novel pathways by which cognitive neuroscientists and rehabilitation clinicians can apply new findings of central nervous system

plasticity towards optimal treatment outcomes for patients with disorders of the brain affecting higher thought processes.

The NINDS, NIA and NIMH have joined efforts on the trans-NIH initiative, "Cognitive and Emotional Health: The Healthy Brain Project," the overall goal of which is to assess the state of longitudinal and epidemiological research on demographic, social and biologic determinants of cognitive and emotional health in aging adults and the pathways by which cognitive and emotional health may reciprocally influence each other.

In addition to studying the neural basis of cognitive functions in the healthy brain, NINDS also supports research to understand the effects of conditions such as stoke, multiple sclerosis, traumatic brain injury, epilepsy, and HIV/AIDS on cognitive processes. In May 2002, NINDS and three other NIH institutes issued a program announcement with set-aside funds (PAS) for "Basic and Translational Research on the Cognitive Sequelae of Parkinson's Disease" to understand the underlying neurobiological mechanisms associated the deficits in executive function, memory, learning, and other cognitive processes in patients with Parkinson's Disease.

NINDS intramural researchers are also conducting a wide range of research to understand the functions of the human brain including cognitive neuroplasticity, social cognition, memory, amnesia, and learning. They use a range of techniques including behavioral measures and imaging technologies to support their research on the neurobiology of higher cognitive functions and other complex behaviors.

Item

Down syndrome - Down syndrome is caused by extra genetic material on the 21st chromosome. It is the leading genetic cause of mental retardation in humans. The Committee urges the NINDS to increase funding for research of Down syndrome, particularly as it relates to cognitive enhancement. The Committee urges NINDS to coordinate these efforts with other Institutes working on related activities, including NICHD, NIA, NHGRI, and NIMH. (p.122)

Action taken or to be taken

The NINDS is actively engaged in supporting research to address Down syndrome, the most frequent cause of mild to moderate mental retardation. The Institute funds research focused on understanding the neuroanatomical and physiological abnormalities in Down syndrome, the genetic and molecular basis for the degeneration of specific neuronal populations in the brains of elderly Down syndrome patients, and the role of different genes in various aspects of Down syndrome. In the last four years, NINDS funding for Down syndrome research has more than doubled.

In addition to the research it supports, NINDS was one of the sponsors of the "10th International Meeting on the Molecular Biology of Chromosome 21 and Down Syndrome," held in September 2002 in Spain. Presentations at this meeting included research on a genetic analysis of chromosome 21; downstream targets of genes and the molecular pathways involved in the

disorder; neuropsychology of Down syndrome; research using mouse models of the disorder; and future directions in research.

Other Institutes at NIH also support activities relevant to Down syndrome. The National Institute of Mental Health (NIMH) supports research on mental illness in the context of mental retardation, including Down syndrome. The NIMH, together with the NICHD, issued a program announcement (PA-01-028) in December 2000 entitled, "Research on Psychopathology in Mental Retardation," that invites applications for research designed to elucidate the epidemiology, etiology, treatment, and prevention of mental disorders, including emotional and behavioral problems, in persons of any age with mental retardation. This PA is in the process of being reissued.

The National Institute on Aging (NIA) supports a wide portfolio of research on understanding the relationship between Down syndrome and Alzheimer's disease (AD). Patients with Down syndrome over the age of 40 show neuropathological features of AD, including the degeneration of a subset of neurons in the forebrain. The intramural research program at NIA also conducts research on understanding the neurodevelopmental defects and neurodegenerative processes that contribute to Down syndrome.

The NINDS will continue to support and enhance its Down syndrome research, including relevant aspects of cognitive enhancement, and will coordinate its efforts with these and other NIH institutes to help advance research on Down syndrome and other related disorders.

Item

Dushenne Muscular Dystrophy - The Committee commends NINDS for initiating the muscular dystrophy cooperative research centers. The Committee expects NINDS to work cooperatively with NIAMS and NICHD to expand the scope and level of research undertaken by the centers program. (p.123)

Action taken or to be taken

The MD-CARE Act mandated that NIH establish centers of excellence for MD research. In September 2002, NIH issued the request for applications (RFA) "Muscular Dystrophy Cooperative Research Centers," to establish research centers, and in October 2003, following peer review of the submitted applications, NIH issued awards to establish three MD Cooperative Research Centers. The NIAMS, NICHD, and NINDS will each fund one center at up to one million dollars in direct costs per center per year for five years. Projects at the three centers will include studies on Duchenne, myotonic, and facioscapulohumeral muscular dystrophies, and will investigate therapeutic approaches including stem cell and gene therapy. The Centers will also offer training opportunities for muscular dystrophy (MD) researchers. In FY 2004, NIH plans to re-issue the RFA for cooperative research centers, and expects to fund up to two additional meritorious centers in FY 2005.

The Muscular Dystrophy Association (MDA) has agreed to commit up to $1.5 million to enhance research activities at each of the three Centers funded by NIH ($500,000 per center per year for

three years). The NIAMS, NINDS, and NICHD signed a Memorandum of Understanding (MOU) with MDA in May 2003 to formalize this partnership. The principal investigators of each center have been invited by MDA to apply for these funds, and MDA expects to make awards of the supplements in 2004.

The NINDS will continue to work collaboratively with NIAMS and NICHD on the Centers program. In accordance with the "Muscular Dystrophy Cooperative Research Centers" RFA, a steering committee to insure overall coordination of the MD Cooperative Research Centers program is being formed, and will include the scientific program officers from NIAMS, NINDS, and NICHD. However, the Centers program is only one of the many ways that NINDS, NIAMS, and NICHD are working together to further MD research. All three institutes are represented on the Muscular Dystrophy Coordinating Committee (MDCC), which held its first meeting on July 1, 2003, and is in the process of developing a research and education plan for MD. In recent years, the three institutes have worked together to co-sponsor initiatives and workshops on MD. It is important that NIH use its resources to continue to support a wide range of activities on MD; such a multi-faceted approach will likely yield the most significant advances in understanding and treating the muscular dystrophies.

Item

Dystonia - The Committee continues to support the expansion of research and treatment developments regarding the neurological movement disorder dystonia, given that dystonia is the third most common movement disorder after tremor and Parkinson's disease. The Committee encourages NINDS to support additional research on both focal and generalized dystonia, and commends NINDS for its study of the DYT1 gene and encourages expansion in this research area. In addition, the Committee requests NINDS be prepared to report on it at the fiscal year 2005 budget hearings. (p 123)

Action taken or to be taken

Please refer to page NINDS - 33 of this document for NINDS response to this item regarding dystonia.

Item

Epilepsy - The Committee encourages NINDS to expand its research efforts into the prevention, treatment, and eventual cure of epilepsy. In particular, the Committee urges the Institute to focus on the critical research issues relating to the 30 percent of patients with intractable epilepsy, the life-long impact of seizures on young children, and the growing incidence of epilepsy in the elderly. The Committee encourages the Institute to continue its anti-epileptic drug development program, including research on therapies for the large number of people not responding to current treatment. (p.123)

Action taken or to be taken

Please refer to page NINDS - 29 of this document for NINDS response to this item regarding epilepsy.

Item

Juvenile diabetes - The Committee commends the NINDS for its efforts to prevent and treat hypoglycemia and neuropathy, both of which are serious complications of diabetes and demonstrate accelerated development in individuals with juvenile diabetes. The Committee encourages the NINDS to expand its research in neuropathy and to consider establishing centers specifically for the detection and prevention of this dangerous complication of diabetes. (p.123)

Action taken or to be taken

Please refer to page NINDS - 36 of this document for NINDS response to this item regarding juvenile diabetes.

Item

Learning Disabilities - The Committee commends NINDS for the work conducted to explore the neurological aspects of learning disabilities. We look forward to learning the results of this work and encourage the Institute to continue to coordinate with other Institutes working on related activities. (p. 123)

Action taken or to be taken

Learning disabilities are disorders that affect the ability to understand or use the spoken or written language, do mathematical calculations, coordinate movements, or direct attention. Defects in neurological development may result in neurobehavioral deficits such as learning disabilities.

NINDS-funded researchers are studying the neurological basis of a number of pediatric disorders that result in cognitive defects. The NINDS funds a multi-disciplinary center at the University of California, San Diego to explore the neural bases of language and cognitive development from seven to eighteen years of age. Another NINDS-funded project is investigating neurocognitive development in boys diagnosed with Duchenne muscular dystrophy. The project seeks to understand if there is a genetic basis to the impairment of verbal and immediate memory skills, and, in some cases mental retardation, in boys with Duchenne muscular dystrophy. NINDS-funded researchers are also studying developmental abnormalities, including delays in neuropsychological function, decreased intelligence, and impaired cognition in children with epilepsy. The Institute also funds research on other disorders that may result in learning disabilities, including fragile X syndrome, attention deficit disorder, Down syndrome, dyslexia, autism, and tuberous sclerosis. This research may aid in determining the most appropriate strategies to treat many of the symptoms of these disorders, including deficits in cognitive development.

The NINDS works collaboratively with other NIH institutes that fund research on learning disabilities, including the National Institute of Mental Health (NIMH) and the National Institute of Child Health and Human Development (NICHD). These institutes have jointly sponsored meetings and initiatives in the past few years on a number of the disorders mentioned above.

The NINDS will continue to work together with these institutes and others, with an interest in learning disabilities, to further research in this area.

Item

Mucopolysaccharidosis (MPS)– The Committee is encouraged by NINDS sponsorship of a scientific conference focusing on central nervous system issues and the barriers to and development of effective therapies for MPS disorders. The Committee urges NINDS to solicit and provide for investigator proposals resulting from the findings of this conference. The Committee encourages NINDS, in collaboration with NIDDK and NICHD, to support current MPS research and study of the blood brain barrier as an impediment to treatment, and to use all available mechanisms to further stimulate and enhance efforts to better understand and treat MPS disorders (p.123).

Action taken or to be taken

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

Item

Neurofibromatosis.--Advances in NF research have linked NF to cancer, brain tumors, learning disabilities and heart disease. Because NF regulates both the RAS and cAMP pathways relating to cell growth and cognition, NF plays a pivotal role both in disorders of the brain and in cancer. The enormous promise of NF research is now reaching fruition in the testing of potential therapies. Therefore, the Committee encourages NINDS to expand its NF clinical and basic research portfolios through clinical trials, RFAs, and other funding mechanisms to accelerate and exploit the tremendous progress in NF research. The Committee commends NINDS for its leadership role in NF research and in coordinating efforts with other Institutes engaged in NF research and encourages the NINDS to work in partnership with the NF research community, including patient advocacy groups, in identifying and pursuing scientific opportunities that will ultimately allow for the development of effective treatments for NF (p. 123).

Action taken or to be taken

Please refer to page NINDS - 36 of this document for the NINDS response to this significant item regarding neurofibromatosis.

Item

Pick's Disease – The Committee urges the NINDS in conjunction with NIA to increase research efforts on Pick's Disease and other frontotemporal dementias. The Committee further urges the Institutes to consult with researchers, clinicians, and patient advocates and report to the Committee on progress being made in this field of research. (p. 124)

Action taken or to be taken

Although Pick's disease is a rare condition, there are some important biological features that link Pick's and other forms of frontotemporal dementia (FTD) to the more common causes of dementia, such as Alzheimer's disease. One of these features is a disturbance in the protein tau.

Inside neurons, tau is associated with the cellular skeleton of the axon – the neuronal structure that conveys information between cells in the nervous system. Mutations in, and disturbances of, tau can have serious repercussions on the transmission of nerve impulses in particular areas of the brain, and can contribute to the development of dementia. Although the abnormal changes in tau that are observed in the brains of individuals with Pick's are different from those in Alzheimer's disease, research on tau can have implications for both disorders.

The NINDS is currently funding several studies on the tauopathies, including the development of a fruit fly model that will enable researchers to better understand the mechanisms through which the aggregation or "clumping" of tau occurs, the characterization of the effects of mutant tau and other gene mutations that contribute to FTD, and the study of normal tau and its relationship to microtubules – the tube-shaped proteins that help give nerve cells their stability. NINDS is also planning to help support a workshop on the FTDs, including Pick's disease, in July 2004, that would explore the cognitive and neuropathological aspects of FTDs, imaging studies of these diseases, and the role of genetics. In addition to these efforts, NINDS will also continue to seek opportunities to work with NIA on program activities related to Pick's disease and other FTDs.

Item

Spinal Muscular Atrophy- Spinal Muscular Atrophy (SMA) is the most common genetic killer of infants and toddlers and is the most prevalent genetic motor neuron disease. While there is currently no cure for the disease, the research outlook is promising. Researchers have already identified the genes involved in SMA as well as compounds that may lead to potential treatments. The Committee understands that the severity of the disease, its relatively high incidence, and the possibility of imminent treatments have led NINDS to select SMA as a model for a new approach to funding translational research. The Committee strongly endorses that plan. The Committee urges NIH/NINDS to equip the program and the personnel charged with executing the plan with appropriate authoritative and financial resources to maximize the chances of success. (p.124)

Action taken or to be taken

The NINDS remains committed to supporting the collaborative program to accelerate therapeutics development for spinal muscular atrophy (SMA). To facilitate this effort, the Institute has developed a performance and milestone-based mechanism that may also serve as a model for other diseases. The primary contract to provide overall scientific and organizational support was awarded in September 2003. The Steering Committee, whose membership is drawn from academia and industry, held an intensive meeting on September 17, 2003, and developed a research plan and priorities for the research projects conducted under the contract. The research plan and first solicitation for research sub-contracts were publicized in November 2003; the first research project is expected to be funded during March 2004. The Institute will submit a progress report, as requested, on all aspects of SMA translational research in March 2004. The NINDS support for this important effort is on-going.

Item

Stroke—The Committee commends the NINDS for convening a Stroke Progress Review Group. The Group's report identifies critical gaps in stroke knowledge and outlines 5 research priorities and 7 resource priorities. The Committee urges the Institute to implement the priorities of the Progress Review Group. (p. 124)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) continues to support a broad portfolio of basic, clinical, and population-based research on the causes, biology, prevention, early detection, and treatment of, as well as recovery from, stroke. In addition, since the publication of the Stroke Progress Review Group (SPRG) Report in April 2002, the NINDS taken steps to address the research and resource priorities identified by the SPRG. To coordinate the implementation effort, the Institute formed a Stroke Working Group (SWG), consisting of NINDS program staff with a shared interest in stroke research and expertise in basic research, clinical studies, brain vasculature, neuronal injury, and genetics. The SWG meets on a biweekly basis to review recent progress, and to discuss and plan for future activities. The NINDS has also undertaken a number of initiatives designed to address the Report's research and resource priorities. For example, to address the research priority to identify and isolate the genes and proteins underlying stroke, NINDS has issued a initiative to encourage gene discovery for complex neurological disorders, including stroke. The Institute has also established the NINDS Human Genetics Resource Center, which is a repository of DNA samples, immortalized cell lines (from which DNA can be extracted continuously), and accompanying clinical and pedigree data, which will be an invaluable resource to researchers; stroke is among the first group of disorders to be included in the repository. Another research priority emphasized the importance of a better understanding of the blood-brain barrier, and NINDS has issued an initiative to encourage research in this area . In the area of resources, one of the priorities listed was to develop and apply emerging gene microarray technologies to the field of stroke. Gene microarrays are research tools that allow researchers to measure the activity of large numbers of genes at the same time. To address this priority, NINDS has established microarray centers to assist researchers, including stroke researchers, in utilizing this technology.

In January 2003, NINDS met with the SPRG to update it on NINDS implementing activities, and to discuss future needs and opportunities. SPRG members discussed the continued importance of many of the priority areas identified in the Report, including: creation of networks and facilitation of collaborative research; facilitation of translational research; database tools and data sharing issues; and promotion of training opportunities, among other others. The NINDS intends to convene meetings of the SPRG periodically, in order to review progress and continue the prioritization of its recommendations.

In addition to specifically addressing priority areas identified by the SPRG Report through initiatives and other program activities, the NINDS will continue to encourage investigator-initiated research, to ensure that stroke is part of relevant trans-Institute initiatives (e.g., for

resources or training), and to collaborate with other agencies and organizations that have a shared interest in stroke research.

Item

Tremor – The Committee has been made aware of the very common condition of essential tremor affecting millions of Americans and causing significant physical and social disability. Its case and underlying pathological basis is unknown. Very little basic or clinical research on this disorder is currently being undertaken. It appears that new research such as technical imaging and chemical analysis may offer promise in shedding light on this mysterious and common disorder. The Committee was pleased to learn that NINDS supports a tissue bank for essential tremor and the Committee looks forward to learning of the Institute's assessment of research opportunity and of progress through expansion of other relevant research efforts. (p.124/125)

Action taken or to be taken

The NINDS is committed to exploring the causes and treatments of essential tremor, and is currently funding several studies that use a variety of approaches to this end. For example, researchers have identified several chromosomal regions that may influence the development of tremor, but to date they have not found any specific gene mutations that predispose affected individuals to develop this condition. As a result, two separate groups of NINDS-supported researchers are attempting to gather more families that have this condition in order to isolate and characterize genetic mutations that may contribute to tremor, and to identify additional chromosomal regions of interest. Other NINDS-funded researchers are exploring environmental exposures that contribute to the development of tremor, since genetics are probably only partially responsible in most affected individuals, and are also studying the use of imaging techniques to evaluate how deep brain stimulation helps control tremor. Lastly, researchers at an NINDS-funded brain bank will use human tissue samples to determine if some regions of, or systems in, the brain are selectively affected in individuals with essential tremor. All of these studies have the potential to accelerate the development of treatments for this common, but debilitating, neurological condition.

FY 2004 Conference Report Language (Conf. Rpt. 108-401)

Item

Research into gender and immunity – The conferees are also pleased to note a major success in past years in the creation of a joint collaborative research program in "gender and immunity" between the National Institute of Allergy and Infectious Diseases (NIAID) and a major voluntary association for the disease, in which NINDS participates. The conferees encourage NINDS to seek similar collaborative activities related to MS. (p. 771)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke has a longstanding interest in supporting research related to multiple sclerosis, and regularly pursues and participates in relevant collaborative activities. The Institute collaborated with the National Multiple Sclerosis Society (NMSS), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the Office of Research on Women's Health (ORWH) in issuing the Request For Applications (RFA) on "Sex-based Differences in the Immune Response" (RFA-01-005) in February 2001. As a result of this collaborative effort, fourteen research projects were funded in fiscal year 2003; three of these projects were relevant to the central or peripheral nervous system and were supported by NINDS.

In January 2002, NINDS collaborated with three other Institutes (including the National Institute for Mental Health (NIMH), the National Institute of Drug Abuse (NIDA), and NIAMS) in a program announcement (PA) entitled, "Identifying Functional Links Between the Immune System and Brain Function Including Behavior" (PA-02-045). During FY2003, four research projects were funded as a result of this solicitation; two were supported by NINDS.

In September 2003, NINDS co-sponsored an international workshop in conjunction with the National MS Society focused on genetics and multiple sclerosis. Multiple sclerosis is a complex genetic disorder, meaning no single gene is responsible for disease induction or progression. Despite four whole genome screens and a large number of candidate gene searches, concrete evidence for MS susceptibility genes is still elusive. The purpose of this workshop was to explore possibilities for the creation of a collaborative MS genetics network that will share strategies, reagents, methods, data and samples to accelerate the discovery of MS susceptibility genes.

Most recently, NINDS cooperated with NIAID, NIAMS, the National Institute of Dental and Craniofacial Research (NIDCR) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to re-issue "Hyperaccelerated Award/Mechanisms in Immunomodulation Trials" (RFA AI-04-001). Twelve projects were funded through the original solicitation (RFA AI-02-003) , including an NINDS supported project relevant to MS.

Item

Duchenne muscular dystrophy clinical trials – The conferees urge NINDS, in collaboration with the National Institute on Arthritis and Musculoskeletal and Skin Diseases and the National Institute of Child Health and Human Development, to accelerate clinical trials to improve treatment for patients with Duchenne muscular dystrophy. The conferees encourage NINDS to actively seek and assess clinical trial proposals and to expedite the review process for clinical research in Duchenne muscular dystrophy. The conferees strongly encourage the funding of three additional centers of excellence by the end of fiscal year 2004. (p. 771)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS), along with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Child Health and Human Development (NICHD), are committed to improving the treatment of patients with muscular dystrophy (MD). Clinical research is an important component of the recently established Muscular Dystrophy Cooperative Research Centers (MDCRCs). These centers - which are being funded by NINDS, NIAMS, and NICHD - support an integrated basic and clinical research program focused on improving knowledge and treatment of MD. The centers are designed to accelerate the translation of fundamental scientific advances to the clinic through close interaction between basic researchers and clinicians. Two of the centers, at the University of Pittsburgh and the University of Washington, have a particular focus on the Duchenne form of MD.

The NIH has taken other proactive steps to advance clinical and translational research on muscular dystrophy (MD). In January 2001, NINDS and NIAMS issued a program announcement with set-aside funds entitled "Therapeutic and Pathogenic Approaches for the Muscular Dytrophies," in which the institutes expressed their intent to commit approximately $5 million in total costs to fund applications during fiscal years 2002 to 2004. This solicitation has already resulted in a number of funded projects designed to advance treatment interventions for MD. One study, a clinical trial funded by NINDS, is testing whether the common antibiotic gentamicin has therapeutic potential for patients with both the Duchenne and limb-girdle forms of MD. This trial may provide new insights that will help shape the course of future clinical studies in this area. Other studies funded as a result of this initiative focus on bridging the gap between basic research and clinical trials. This "translational" research is needed to determine the most promising clinical strategies to bring to trial. For example, studies funded by NINDS and NIAMS are aimed at improving gene therapy for Duchenne MD, including gene vector design and vector delivery methods. Another project funded by NINDS uses an animal model to study the efficacy of the protein biglycan as a therapeutic agent for Duchenne MD. The NIH continues to welcome new proposals for translational and clinical research aimed at treating and delaying the progression of MD and related neuromuscular diseases.

The NIH will continue its efforts to further basic, translational, and clinical research in MD in the coming years. During fiscal year (FY) 2004, the NIH plans to re-issue the solicitation for the MDCRCs, and expects to fund up to two additional centers - one each by NIAMS and NINDS - in FY 2005 as a result of this initiative, for a total of up to five centers. It is important to note that the MDCRC program is only one of the many ways that NINDS, NIAMS, and NICHD are working together to further MD research. In recent years, the three institutes have worked together to co-sponsor initiatives and workshops on MD. All three institutes are represented on the Muscular Dystrophy Coordinating Committee (MDCC), which held its first meeting on July 1, 2003, and is in the process of developing a research and education plan for MD. It is critical that NIH use its resources to continue to support a wide range of activities on MD; such a multi-

faceted approach will likely yield the most significant advances in understanding and treating the muscular dystrophies.

Item

Stroke in women – . . . . The conferees further urge NIH to increase research into new therapies for stroke in women as well as ways of enhancing the vascular health of all Americans, including (1) a clinical trial of carotid endarterectomy and angioplasty/stenting in women, (2) observational research on differences in the way men and women present with stroke symptoms, and (3) studies of differences in how men and women respond to FDA-approved antiplatelet agents for recurrent stroke prevention. (p. 771-772)

Action taken or to be taken

The NINDS supports a broad range of both basic and clinical studies on stroke, and therapeutic and preventative interventions for stroke, including stroke in women. The incidence of cardiovascular disease in women increases dramatically following menopause, and this may be triggered by estrogen loss. The NINDS is currently funding a number of studies in animal models of the role of estrogen in protecting brain cells from injury caused by stroke. In addition, other investigators are trying to establish a link between estrogen and brain control of blood pressure, which when elevated, is a risk factor for stroke.

Anecdotal evidence over the last several years had suggested that hormone therapy in menopausal women may confer some protection against heart disease and stroke. In 2001, the NINDS-sponsored trial, Women's Estrogen for Stroke Trial (WEST), showed that estrogen replacement therapy does not reduce the risk of stroke or death in postmenopausal women who have already had a stroke or a transient ischemic attack. In addition, in 2002, investigators involved in the Women's Health Initiative, a large NIH-funded controlled clinical study, reported that they had found small increases in breast cancer, coronary heart disease, stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo pills. For these reasons, the study was halted. Further research will be needed to explain the differences seen in animals that were not replicated in human studies, and to further clarify the role of estrogen in stroke in women.

Carotid stenosis, or narrowing of the carotid artery, is a major cause of stroke. The NINDS has supported several major clinical trials testing the efficacy of a surgical procedure for carotid stenosis called carotid endarterectomy, to prevent both initial and recurrent stroke, including the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Artery Stenosis Collaborative Study (ACAS). Both these trials included women as participants, and data analysis suggested that women may not benefit from carotid endarterectomy as much as men mainly due to a higher surgical complication rate. A current ongoing NINDS funded trial, the Carotid Revascularization Endarterectomy vs. Stenting Trial

(CREST), will directly compare the efficacy of carotid endarterectomy to angioplasty/stenting, a newer less invasive surgical method, and has been designed to specifically examine gender differences in the efficacy of the two procedures.

There is some evidence that there may be gender differences in how men and women present with stroke symptoms. A recent study from the lab of an NINDS-funded investigator showed that women present more frequently with non-traditional stroke symptoms compared to men, displaying pain, changes in level of consciousness, and disorientation as well as other, non-neurologic symptoms. This is an important finding, since it suggests that recognition of these gender differences by medical personnel might lead to faster determination of stroke occurrence in women, leading to better treatment outcomes.

The NINDS has supported a number of clinical trials testing the efficacy of both antiplatelet and anticoagulation therapies for the prevention of both initial and recurrent strokes in both men and women. For example, the Stroke Prevention in Atrial Fibrillation (SPAF I, II, III) trials examined the effectiveness of aspirin and warfarin in preventing a first stroke in patients with atrial fibrillation. Atrial fibrillation is a common type of irregular heartbeat that is a risk factor for stroke, especially among elderly women. These trials showed that women benefitted more from anticoagulation therapies such as warfarin compared to men. In addition, a recent meta-analysis of clinical trials for both antiplatelet and anticoagulation therapies demonstrated that there were no gender differences in the effectiveness of aspirin for prevention of stroke.

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2004 Amount Authorized	2004 Final Conference	2005 Amount Authorized	2005 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$1,470,942,000	Indefinite	$1,515,277,000
National Institute of Neurological Disorders and Stroke	Section 457-459	42§285j	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	29,751,000	b/	30,346,000
Total, Budget Authority				1,500,693,000		1,545,623,000

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

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
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 3/
1998	722,712,000 2/	763,325,000	781,351,000	(780,713,000)
1999	815,649,000 2/4/	851,066,000	903,278,000	903,278,000
Rescission				(598,000)
2000	890,816,000 2/	979,281,000	1,019,271,000	1,034,886,000
Rescission				(5,510,000)
2001	1,050,412,000 2/	1,185,767,000	1,189,425,000	1,176,482,000
Rescission				(383,000)
2002	1,316,448,000	1,306,321,000	1,352,055,000	1,328,188,000
Rescission				(1,522,000)
2003	1,432,305,000	1,432,305,000	1,466,005,000	1,466,005,000
Rescission				(9,529,000)
2004	1,468,926,000	1,468,926,000	1,510,926,000	1,510,776,000
Rescission				(9,569,000)
2005	1,545,623,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
3/ Excludes enacted administrative reduction of $339,000
4/ Reflects a decrease of $2,457,000 for the budget amendment for Bioterrorism.

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Office of the Director	68	72	71
Division of Extramural Activities	126	117	117
Division of Intramural Research	414	407	407
Total	608	596	595
FTEs supported by funds from Cooperative Research and Development Agreements	(2)	(2)	(2)

FISCAL YEAR	Average GM/GS Grade
2001	10.3
2002	10.7
2003	11.2
2004	11.2
2005	11.2

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Detail of Positions

GRADE	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
ES-6	1	1	1
ES-5	0	0	0
ES-4	3	2	2
ES-3	0	0	0
ES-2	0	0	0
ES-1	0	1	1
Subtotal	4	4	4
Total - ES Salary	$0	$0	$0
GM/GS-15	39	39	39
GM/GS-14	49	52	52
GM/GS-13	60	57	57
GS-12	68	71	75
GS-11	53	53	50
GS-10	8	5	6
GS-9	41	46	50
GS-8	28	26	22
GS-7	36	40	41
GS-6	4	4	3
GS-5	4	4	4
GS-4	4	4	4
GS-3	2	2	2
GS-2	1	1	0
GS-1	0	0	1
Subtotal	397	404	406
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	4	4	4
Senior Grade	3	4	5
Full Grade	2	2	1
Senior Assistant Grade	1	0	0
Assistant Grade	0	0	0
Subtotal	10	10	10
Ungraded	188	188	188
Total permanent positions	397	402	402
Total positions, end of year	599	599	599
Total full-time equivalent (FTE) employment,end of year	608	596	595
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$142,500	$146,900	$151,420
Average GM/GS grade	11.2	11.2	11.2
Average GM/GS salary	$68,531	$70,640	$72,812