DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

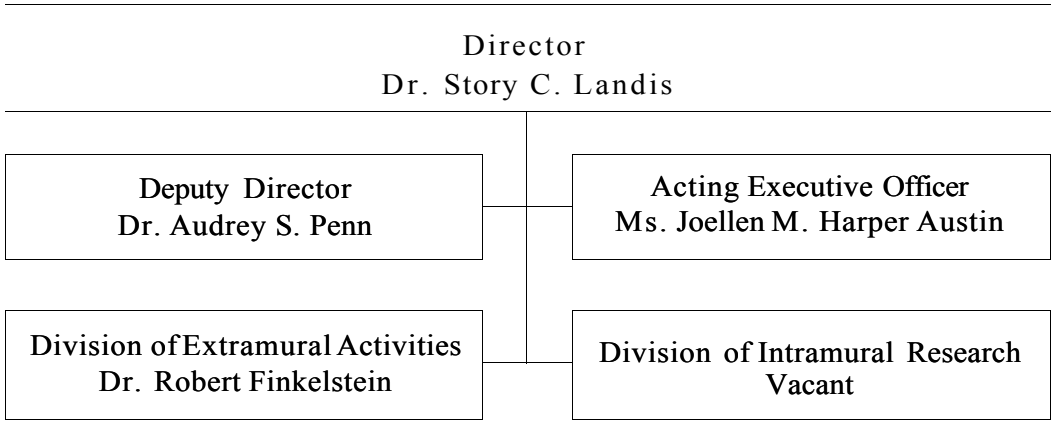
National Institute of Neurological Disorders and Stroke

FY20Q6 Budget

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Organizational Chart



NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

For carrying out section 301 and title IV of the Public Health Service Act with respect to neurological disorders and stroke, [*1,552,123,000]57,550,260,000.*

[Department of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Consolidated Appropriations Act, 2005]

Amounts Available lor Obligation 1/

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$1,510,776,000	Sl.552,123,000	51,550,260,000
Enacted Rescissions	(9,569,000)	(12,675,000)	0
Subtotal, Adjusted Appropriation	1,501,207,000	1,539,448,000	1,550,260,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	(2,942,000)	0	o
Comparative transfer to NIBIB foT Radiology Program	(92,000)	0	0
Comparative transfer to Buildings and Facilities	(422,000)	0	0
Comparative transfer to/from other NTH ICs for NIH Roadmap	2,942,000	0	0
Subtotal, adjusted budget authority	1,500,693,000	1,539,448,000	1,550,260,000
Unobligated balance lapsing	(62,000)	0	0
Total obligations	1,500,631,000	1,539,448,000	1,550,260,000

JV Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004 - $7,573,000 FY 2005 - $8,100,000 FY 2006 - SS, 100,000
Excludes $156,000 in FY 2005 and $219,000 in FY 2006 for royalties.

Justification
National Institute of Neurological Disorders and Stroke

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

Budget Authority:

	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
568	51,500,693,000	563	$1,539,448,000	563	$1,550,260,000	0	510,812,000

This document provides justification for the Fiscal Year 2006 activities of the National Institute of Neurological Disorders and Stroke (NINDS), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2006 HIV/AIDS activities can be found in the N1H section entitled "Office of AIDS Research (OAR)."

Introduction

The mission of the NINDS is to reduce the burden of neurological disease through research to improve prevention and treatment. Hundreds of disorders affect the brain, spinal cord and nerves of the body. They exact an enormous toll in life, disability, and suffering, as well as billions of dollars each year in medical expenses and lost productivity. Although prevention and treatment of neurological disorders are still far from adequate, in the half century since Congress established the Institute, the NINDS has contributed substantially to progress that is improving life for many people. Prevention of stroke and of nervous system birth defects is having a major impact on public health. Better drugs and surgical treatments help relieve symptoms for people with Alzheimer's disease, Parkinson's disease, epilepsy, chronic pain, dystonia, multiple sclerosis, and many other diseases. Improvements in genetic testing and brain imaging also enhance physicians' ability to diagnose disease and guide therapy for nervous system disorders.

Future prospects for preventing and treating neurological disorders are encouraging because of opportunities arising from basic and clinical neuroscience. Emerging strategies include drugs that home in on the specific molecules that cause disease, neuroprotective agents that fend off the insidious destruction of nerve cells, stem cell and regenerative therapies that repair the damaged nervous system, natural "neurotrophic" factors that promote survival and growth of brain cells, vaccines that prevent even non-infectious diseases, implantable devices that compensate for brain circuits unbalanced by disease, therapies that silence 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.

To generate opportunities such as these and bring them to fruition, the NINDS supports a wide spectrum of research to understand the nervous system in health and disease, and to translate that knowledge into prevention and treatment. The Institute supports most research through grants and contracts to physicians and scientists at medical schools, hospitals, universities, private research institutions, and small businesses throughout the country. These extramural

investigators seek out scientific opportunities, propose research projects, evaluate proposals in peer review, carry out research, and help the Institute plan for the future. NINDS intramural investigators conduct research on the NIH campus in Bethesda, Maryland. The NIH campus provides one of the largest communities of neuroscientists in the world and unique resources, including the new Mark O. Hatfleld Clinical Center, a hospital totally dedicated to clinical research, and the NIH Neuroscience Center, which is explicitly designed to integrate neuroscience across disciplinary boundaries. In keeping with its mission, the NINDS also fosters the training of scientists and physicians in basic and clinical neuroscience and serves as a prime source of information for scientists, physicians, government, and the public.

Science Advances

Disorders of the nervous system disrupt essential bodily functions, cause pain and discomfort, and impair vital abilities, from perception and movement through emotions, memory, language, and thinking. Trauma, infections, toxic exposure, degenerative diseases, tumors, gene mutations, systemic illness, vascular events, nutritional deficiencies, and adverse effects of essential treatments for other diseases can all affect the nervous system. Compounding the challenge of confronting these diseases, the brain and spinal cord are intricate in structure, elusive in their normal workings, difficult to access, sensitive to intervention, and reluctant to regenerate following damage. Because of these difficulties, progress is often won in small increments. 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. Years of painstaking research refines each new idea in the laboratory, tests therapies in cells and animals, and evaluates safety and efficacy through clinical trials of increasing size and complexity. The NINDS funds research at every step of this process. The following examples from the thousands of findings published in the past year by NINDS extramural and intramural investigators illustrate the range of ongoing research.

Improving therapies for multiple sclerosis; A small NINDS intramural clinical trial of multiple sclerosis patients who did not respond to interferon, the standard therapy, found that adding daclizumab improved outcome. Daclizumab is a genetically engineered antibody molecule that has previously been used to modify immune responses in kidney transplantation. Patients on daclizumab improved in tests of walking and hand dexterity, and brain imaging showed a 78% reduction in new brain lesions. Further studies are needed to confirm the effectiveness of daclizumab and see whether the drug may work as a stand-alone therapy.

Progress toward cell therapies for demyelmating diseases: Loss of myelin, the fatty substance that ensheathes nerve fibers, is a major problem in several neurological disorders, including multiple sclerosis, brain and spinal cord trauma, and inherited diseases that affect children, such as Canavan, Krabbe, and Tay-Sachs disease. Without myelin, nerve fibers cannot conduct electrical impulses properly. Scientists have now restored myelin widely throughout the brains of a strain of mice born without myclin by injecting highly purified human "progenitor" cells (unspecialized cells that give rise to specialized brain cells). The cells were isolated using a sophisticated sorting technique from adult brain tissue removed during therapeutic surgery.

Toward gene therapies for muscular dystrophy: Researchers have developed a gene therapy method that delivers a therapeutic gene to all of the voluntary muscles of a mouse, overcoming

one of the main obstacles for treating muscular dystrophies. The method, uses a modified (and harmless) vims to carry the gene. Along with the virus vector, the researchers injected a natural regulatory molecule called VEGF that opens blood vessels to passage of the virus. In mice with a gene defect that mimics Duchenne muscular dystrophy, this procedure dramatically improved muscle damage and behavior. Research is underway to determine whether this strategy might be safe and effective for people.

Ultrasound improves stroke drug therapy: Previous NINDS-supported clinical trials showed that the clot-busting drug t-PA (tissue plasminogen activator), when administered within 3 hours of ischemic stroke, can greatly improve a patient's chance for recovery. Ischemic strokes, the most common type of stroke, are caused by blockage of blood flow to the brain. Since 1996, t-PA (tissue plasminogen activator) has been the only FDA-approved therapy for acute ischemic stroke. An NINDS clinical trial of 126 patients has now shown that using ultrasound in combination with t-PA can improve the effectiveness of this drug in breaking up clots and restoring blood flow to the brain. Additional research will standardize the combined therapy and study it in a **larger** group of patients.

Estrogen and autoimmune disease: Women affected by autoimmune diseases like multiple sclerosis often experience an improvement in their symptoms during pregnancy. Scientists and physicians have long suspected that estrogen, a hormone that dramatically increases and remains at high levels during pregnancy, might be responsible for the improvement of symptoms. New research on estrogen's effects on the immune system suggests thai the hormone does indeed cause an increase in the number of immune regulatory T cells that protect against autoimmunity. These findings suggest that estrogen-like compounds could be an effective approach to controlling the inflammation associated with autoimmune disorders.

Fruit flies help reveal what goes wrong in Down syndrome: Scientists know that an extra copy of chromosome 21 causes Down syndrome, but the underlying mechanism of the mental retardation remains mysterious. To study this mechanism, researchers turned to the fruit fly, which has many advantages for experimental studies. Over activity of the fly's version of a particular human chromosome 21 gene perturbed a signaling molecule called calcineurin and produced learning defects. The research team subsequently found similar changes in calcineurin in tissue from people with Down syndrome, illuminating at the level of molecules a process that may be critical for understanding and developing treatments for learning problems in Down syndrome.

Combination therapies improve recovery from spinal cord injury in rats: Over the past decade, scientists have identified several factors that hinder recovery following spinal cord injury, but addressing each of these obstacles individually has had limited beneficial effect in animal models of spinal cord injury. In the past year, three reports demonstrated encouraging progress treating spinal cord injury in rats by combination therapies that simultaneously address multiple factors preventing regeneration in the spinal cord. The three teams used different treatments, as well as different types of spinal cord injury, time frames, and measures of recovery, but each team showed better recovery of function from combination therapies than from any one therapy alone. Although there are significant hurdles before it is appropriate to test these procedures in people, a consensus is emerging that combination therapies may be the best approach for treating spinal cord injury.

New therapeutic strategy! for Alzheimer's disease; A hallmark of brain damage caused by Alzheimer's disease is abnormal accumulations of protein called amyloid plaques. Researchers have now found a drug, called an ACAT inhibitor, that decreases the deposition of plaques by nearly 90% in mice which carry a gene that causes Alzheimer's disease in people. The drug treatment also improves cognitive performance in some mice. Although the experimental drug used in these studies is not appropriate for use in people, another drug that appears to act by the same mechanism is already being investigated for human use to prevent cardiovascular disease. Researchers are now testing whether this drug also reduces plaques in Alzheimer's mice.

Fish in the diet may help protect from Alzheimer's disease: Specific gene defects can directly cause Alzheimer's disease, but for most people with the disease an interaction of genetic susceptibility with environmental factors is responsible, Following hints from epidemiological studies, scientists have found that dietary docosahexaenoic acid (DHA, an omega-3 fatty acid found in fish) protects genetically susceptible mice from an Alzheimer's-like disease. The findings support the idea that increasing dietary DHA might protect against Alzheimer's disease, particularly in people who are genetically most susceptible to the disease.

Brain imaging may help identify high risk stroke patients: Using magnetic resonance (MRI) brain imaging technology, NINDS intramural researchers have linked early changes in the blood-brain barrier to a stroke patient's outcome. The blood-brain barrier normally protects sensitive brain cells from potentially harmful substances in the general circulation. This study showed that patients who had disruption in the blood-brain barrier were more likely to experience bleeding in the brain and have a poor clinical outcome. This technique could eventually help to identify which patients are likely to do the best with emergency stroke therapies designed to unblock blood vessels and restore blood flow to the brain. These therapies can be effective, but carry a risk of bleeding in the brain in some patients.

Gene for rapid-onset dystonia parkinsonism found: Dystonia is a common group of movement disorders in which involuntary muscle contractions often produce twisting, abnormal postures, or repetitive movements. These can be quite painful and disfiguring. Researchers have identified the gene defects responsible for a rare inherited form of dystonia known as rapid-onset dystonia parkinsonism (RDP), that usually strikes suddenly in adolescents or young adults. RDP is unusual in that it often follows a fever, prolonged exposure to heat or exercise, childbirth, or emotional stress, but once symptoms occur they persist. The protein affected by the gene defect normally pumps potassium and sodium ions into and out of cells to maintain their proper concentrations when nerve cells are active, so one possibility is that the pump cannot keep up in stressful circumstances. Future studies will determine how mutations in the gene cause susceptibility to RDP and might provide clues to other forms of dystonia, parkinsonism, or epilepsy.

Vitamin D may help prevent multiple sclerosis in women: An investigation based on analysis of the 20 year Nurses Health Study I and the 10 year Nurses Health Study II has found that women who supplement vitamin D intake through multivitamins are 40 percent less likely to develop multiple sclerosis than women who do not take supplements. The effect of vitamin D on multiple sclerosis must be confirmed with additional research, which is underway.

Genes and cerebral blood vessel abnormalities: Cerebral cavernous malformations (CCM) are abnormalities in blood vessels of the brain that place people at high risk for strokes caused by bleeding in the brain, for severe headaches, and for various neurological deficits. In 1999 scientists discovered the first of what appear to be three genes in which defects can cause this disorder, and this year they have identified the second. The identification of these genes will lead to tests that allow more people with a family history of CCM to be tested. For people who show no symptoms but carry a high risk for serious problems CCV can cause, this may enable substantial improvement in medical care.

Growth factors and SBMA: Scientists have determined that a reduction in the natural growth factor VEGF is a critical link by which the gene mutation in X-linked spinal bulbar muscular atrophy (SBMA), or Kennedy's disease, causes the progressively worsening muscle weakness, cramping and atrophy that characterize this disorder. In a first step towards a therapeutic strategy based on this finding, the investigators found that artificially increasing VEGF rescued cells similar to the neurons that are vulnerable in SBMA in a cell culture model of SBMA. Further experiments are underway to test this approach in mice with the SBMA gene defect.

Potential drug for an inherited nerve disorder: Flereditary sensory and autonomic neuropathy type III, also called Riley-Day syndrome or familial dysautonomia, causes degeneration of nerve cells that control digestion, respiration, and the cardiovascular system. In this disease, a mutation in the gene IKBKAP leads to loss of a critical segment of the IKAP protein, leading ultimately to cell degeneration. By screening a set of 1040 drugs compiled for an NINDS drug screening consortium, researchers found that kinetin, a plant **hormone,** increases the production of the full length IKAP protein. Even subtle increases in the level of the protein might lessen the severity of disease.

Better animal model for Parkinson 's disease: Researchers have developed a rat model of Parkinson's disease that better mimics the progressive nature and underlying brain changes of the human disorder. The model uses drugs that inhibit the proteosomc, which is the cells' machinery for degrading and recycling damaged or unneeded proteins. Protein degradation has been implicated in both rare inherited and the more common "sporadic" types of Parkinson's disease in people. The new model will expedite testing of treatments to slow Parkinson's.

Determining how epilepsy develops: Understanding "epileptogenesis," or how epilepsy develops, is a major focus of research to prevent epilepsy. This year research determined that activation of a brain protein designated TrkB, which receives signals from certain brain regulatory molecules, is an essential step in the development of seizure predisposition in an animal model of epileptogenesis. Drugs that block the activation of TrkB present an attractive strategy for preventing epilepsy in people at high risk, such as following head trauma. Another team of scientists found that a single seizure can make subsequent seizures more likely because changes in a particular molecule, the A-type potassium ion channel, render nerve cells more excitable. Ion channels regulate the flow of electrical currents in nerve cells and are also prime targets for drug development.

Correction of gene function in ataxia telangiectasia: Ataxia telangiectasia is an inherited childhood neurodegenerative disease that results from mutations in the A T M gene. In about 14 percent of cases, the mutation creates a "stop" signal in the gene that causes the A T M protein to be truncated and nonfunctional. Researchers have now determined that certain antibiotics (aminoglycosidcs) allow cultured cells to ignore this stop sign and make full length and functional A T M protein. Follow up studies in animals are necessary to determine whether this approach might work in children with this type of A T M mutation. Clinical studies show that a relatively small amount of functional A T M protein can have benefits, so this is a promising strategy. The NINDS is funding a clinical trial of a similar approach for children in which a false stop signal is responsible for Duchenne muscular dystrophy.

Attending to children in the "stroke belt" : Since the 1960's researchers have noted that U.S. stroke mortality rates are higher in a cluster of Southeastern states called the "stroke belt." A new analysis demonstrates that children, as well as adults, in stroke belt states have a higher mortality rate from stroke than children in other states, even when differences in ethnicity are taken into account. This focuses attention on factors that might influence stroke in both children and adults, in addition to known adult risk factors such as hypertension, obesity and smoking.

Replacing lost nerve cells in Parkinson's disease: For people with advanced Parkinson's disease, replacing the dopamine producing brain cells destroyed by the disease may be the best hope. Animal experiments are progressing toward that goal. Recently, researchers derived unspecialized neural cells, called neural progenitor cells, from human embryonic stem cells and implanted these cells into rats with experimental Parkinson's. The animals improved on four different behavioral tests. Autopsy showed that the cells survived and did not produce tumors, but relatively few specialized to become dopamine cells. Another research team has derived dopamine cells themselves from human embryonic stem cells in culture, which might address this problem and facilitate study of how to protect dopamine cells from degenerating.

Silencing harmful genes: In dominantly inherited disorders, a single defective copy of a gene from either parent produces a harmful protein that causes disease. For the first time, in a mouse model of a dominantly inherited neurological disorder, spinocerebellar ataxia (SCA1), researchers have "silenced" the mutant gene copy while leaving the normal gene copy active. The strategy takes advantage of a recently discovered process called R N A interference (RNAi). RNAi may be useful in many disorders. Other research teams have recently found promising results applying RNAi to inactivate a harmful gene in an animal model of an inherited form of A L S (amotrophic lateral sclerosis, or Lou Gehrig's disease) and to silence improperly active genes responsible for proliferation of tumor cells in an animal model of brain tumors.

Understanding how genes and experience sculpt the brain: Genes and experience together shape brain development, but exactly how is only recently becoming evident. In progress on this front, researchers have discovered a gene, called CREST (for calcium-responsive transactivator) that provides a critical link. Experience evokes electrical activity in nerve cells, which activates CREST, which in turn stimulates the growth of nerve cell dendrites, the branches upon which the cells receive input from other brain cells. Although this is just one aspect of a complex process, understanding how experience and genes interact may have important implications in the future for optimizing healthy brain development and preventing developmental disabilities.

Controlling neural stem cells by understanding the stern cell niche: Neural stem cells can self-renew (multiply) and can differentiate (specialize) to form the many types of cells that make up the nervous system. In the body, stem cells are tightly controlled by signals they encounter in their "niche," that is in their immediate natural environment. Researchers studying the interaction of stem cells with cell types in their niche have found that endothelial cells, which line blood vessels, promote self-renewal and inhibit differentiation of the stem cells. These findings will enable researchers to grow large numbers of neural stem cells while retaining their ability to form many types of specialized cells. In the long run, understanding the various influences that make up the neural stem cell niche is necessary not only to control these cells in laboratory culture, but also to ensure that they perform as desired if they are transplanted for therapies and to promote repair by stem cells naturally present in the brain.

Key to nicotine addiction: Using genetically engineered mice, a research team has shown that a particular molecule in nerve cells is the key to the classic signs of nicotine dependence, including reward, tolerance, and sensitization. The motecule, called the alpha-4 subunit of the nicotinic acetylcholine receptor, normally allows nerve cells to respond to the neurotransmitter acetylchohne, but is co-opted by nicotine. Researchers can now begin to follow step by step from alpha 4, the site at which nicotine first affects nerve cells, to trace the subsequent effects that arise from nicotine activation of alpha 4, and perhaps devise better interventions.

Vaccines tor neurological disorders?—A story of discovery

About a thousand years ago, a Buddhist nun in China ground scabs from smallpox victims into a powder, which she blew into the noses of people who had not yet been exposed to the disease. According to contemporary historical accounts, a **few** people died from this early attempt at vaccination, but many others developed immunity to smallpox. In the modem era, research has dramatically refined vaccination for infectious diseases, with an enormous impact on public health. Now, surprisingly, vaccines are showing the potential to prevent or treat non-infectious nemo logical disorders, including stroke, brain tumor, Huntington's, Parkinson's and Alzheimer's disease.

Long-term scientific developments laid the foundation for vaccine approaches to neurological disorders. First is the growth in basic understanding about immune responses and the chemical signals that control the system. A second major advance has been a growing appreciation for the interactions between the nervous and immune systems in health and disease, m particular, there has been substantial progress in understanding how glial cells regulate the environment around nerve cells. These supporting cells of the nervous system, which outnumber nerve cells in the brain by about 9 to 1, can secrete immune regulatory chemicals, interact with immune cells, and participate directly in an inflammatory response. The involvement of inflammation and other immune reactions, arising from within and outside of the nervous system, *in* neurological disorders ranging from trauma to slow neurodegenerative diseases has become a focus of intense scientific interest. Also critical to vaccine strategies, has been the identification of specific molecular steps that underlie diseases in the nervous system.

The strategy for vaccine-like interventions is unique for each disorder. For some neurological diseases, a vaccination, like vaccines for infectious diseases, stimulates immune cells to enhance their ability to clear out disease beyond what the body could normally muster. In NINDS supported studies, for example, researchers trained patients' immune cells to attack glioblastoma, the most deadly form of brain tumor, by exposing the ceils in culture to molecules from the tumor cells, then returning the activated cells to the patient's braia. Although the results of this approach are very preliminary, a small number of people treated in a phase I trial of this therapy lived an average of 2 and a half years, compared to the typical survival of about 7 and a half months for this type of tumor. Another strategy targets the immune activation process itself to suppress the development of inflammatory processes. In studying stroke, researchers found that E-selectin, a molecule on blood vessels,

carries out a crucial step in immune activation processes that contribute to stroke. By targeting E-sclectin with a nasally administered vaccine in stroke-prone rats, NINDS intramural investigators were able to impede the inflammatory process, significantly reducing the frequency and severity of strokes. This strategy is now moving to human clinical trials. Alzheimer's and Huntington's disease present additional examples of emerging vaccination approaches, in each case focusing on particular molecules that have been implicated in the disease process. An industry-funded clinical trial vaccinated against A-beta, a protein that forms clumps, called plaques, in brain cells of people with Alzheimer's disease. Safely concerns halted this first attempt early, but the approach might ultimately be successful. The NINDS is supporting research in non-human primates to develop this strategy. Recent experiments targeting the mutant protein huntingtin in an animal model of Huntington's disease are also encouraging, as are attempts to develop a vaccine that target a molecule implicated in the damage to nerve cells that follows stroke.

The drug glatiramer acetate, which is used to treat multiple sclerosis, is the only vaccine-like therapy for a neurological disease that has so far been approved for people. The NfNDS supported significant basic research on this approach, and continues to support research on other vaccine approaches for multiple sclerosis. Industry developed glatiiamer acetate therapy though FDA approval based on evidence that it is safe and slightly reduces symptoms of the disease. Exposure to this drug appears to modulate (he immune response in a way that is beneficial for diseases like multiple sclerosis that have an autoimmune aspect. In the past year, NINDS supported researchers found in animal experiments that glatiramer acetate may also help protect the brain in Parkinson's disease. Vaccination with this drug apparently modifies the behavior of glial cells, the supporting cells of the brain, so that their responses are more beneficial to the nervous system. Researchers in Europe have demonstrated similar promise of this approach for ALS.

Will vaccines someday protect us from neurological disorders'? It is too soon to tell. The examples described here—and others for trauma, epilepsy and other disorders—are pioneering forays at the frontier of medical science, and the difficulties are formidable. However, even a decade ago the prospect of vaccines to treat or prevent non-infectious neurological disorders seemed decidedly unlikely, and now the possibility is tanlalizingly real.

The NIH Roadmap

Every component of the NIH Roadmap lias potential to advance the treatment and prevention of nervous system diseases. As the first NIH Roadmap projects are getting underway, the relevance to the nervous system is readily apparent in many cases. Thus, one of the first Roadmap awards to encourage interdisciplinary team research is exploring new directions in stroke rehabilitation, two of the four newly funded National Centers for Biomedical Computing have a major focus on the nervous system, and there are new interdisciplinary training progranis in neurodevelopmental toxicology, neurobehavioral development, autism, clinical neuroengineering, and neurocomputational science. Just as important, but perhaps Jess obvious, the bold vision of the Roadmap to address fundamental roadblocks that hamper all of medical science may have a substantial impact on research against neurological disorders. The Structural Biology Roadmap initiative is developing methods to determine the structure of proteins that are embedded in the membranes that enclose all cells. Most drugs now used to treat neurological disorders act, directly or indirectly, on membrane proteins, so this could have enormous implications for the efficiency of drug development in the future. Similar arguments can be made for the path breaking Roadmap efforts in nanomedicine, a rapidly evolving field of medical intervention at the molecular scale for curing disease or repairing tissue, and for other major Roadmap initiatives within the "New Pathways to Discovery" theme. The multi-faceted effort to "Re-Engineer the Clinical Research Enterprise" is also timely for nervous system diseases. The program promises to accelerate clinical testing for new treatment and prevention strategies, which is pivotal for nervous system diseases because of the pace at which new therapies are

moving from basic neuroscience toward clinical application. As the Roadmap effort unfolds, it is complementing the mission specific initiatives of the NINDS and NIH Institutes.

Initiatives

With the guidance of the Congressionally mandated National Advisory Neurological Diseases and Stroke (NANDS) Council, the NINDS emphasizes investigator-initiated research, as is appropriate to the many and diverse challenges posed by neurological diseases. The Institute 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 Congress highlights needs that must be addressed. Through initiatives, as well as by selection of investigator-initiated grants that address issues critical to the NINDS mission, the Institute maintains a balance among basic, translational, and clinical research, across the many neurological disorders, and between short and long-term scientific opportunities. Over the past few years, the Institute has increasingly worked together with other components of NIH and with voluntary health organizations on initiatives. The following are new initiatives planned for fiscal year 2006:

Accelerating therapy development for Tuberou_s_Sclerosis:_ Tuberous sclerosis complex (TSC) is an inherited disorder that affects the brain and other organs. People with TSC not only develop tumors, but also commonly experience epilepsy, often beginning during infancy, as well as mental retardation, autism, and many other problems. The discovery of the gene defects that cause TSC was a major step forward that opened new opportunities for progress. Recognizing this and in response to Congressional interest, the NINDS and the NIH Office of Rare Diseases organized a TSC symposium in 2002 which informed the development of a five-year NIH Research Agenda for TSC in 2003. In implementing the Agenda, the NINDS, together with other relevant NIH components, is soliciting basic, translational, and clinical grant proposals on the development of therapies for TSC. Projects may include identification of suitable drug targets, refinement of animal models, screening of candidate drugs, and clinical studies to identify opportunities for early intervention.

Basic and clinical research on Rett syndrome: Rett syndrome is a severely debilitating neurodevelopmental disorder that affects females. Girls with this disease appear to develop normally until about 6 to 18 months of age, but then regress. They lose speech, hand skills, and cognitive abilities, while also developing seizures, movement disturbances, mental retardation, autism, and other problems. In 2003, following the discovery that mutations in the MeCP2 gene cause most cases of Rett syndrome, the NINDS and the NICHD issued a program announcement to stimulate research in this area. There has been significant progress, including the exciting finding that introducing the MeCP2 protein into nerve cells of adult mice with MeCP2 mutations rescues Rett-like symptoms. In response, the Institute, working together in a public-private partnership with voluntary health organizations, will solicit applications focused on basic research and development of therapies for Rett syndrome that capitalize on this progress.

Stem cells: Over several years, 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 neural stem cells; and to promising therapeutic attempts in animal models of Parkinson's disease, demyelinating diseases, stroke, spinal cord

injury, brain tumor, and several inherited neurological disorders. Research on all aspects of stem cell biology, from basic questions about what controls proliferation and specialization, to pragmatic concerns about transplant therapies, is among the highest priorities of the Institute. This year, the NINDS is coordinating the review of an NIH initiative to create Centers of Excellence in Translational Stem Cell Research. These centers will bring together teams of basic stem cell biologists, clinicians with disease specific knowledge, surgeons with expertise in delivering cells, and scientists with experience in developing and studying animal models. The goal is to expedite translation of basic science advances in stem cell biology into animal model studies, and on to clinical trials. For fiscal year 2006, the NINDS will also solicit research on the interactions between stem cells and the microenvirorunent that they encounter in the brain, which is key for virtually all types of neural stem cells therapies.

Delivery of RNAi therapeutics into the nervous system: RNA interference (RNAi) has emerged as a powerful strategy for silencing genes. This new technology has already had a major impact on basic studies of gene function. Recent findings suggest that RNAi might also be applied, to treating neurological diseases, such as Huntington's disease, familial ALS, and spinocerebellar ataxias, in which a mutated gene harms cells, and brain tumors, in which inappropriate activity of genes allows proliferation of tumor cells. Although the NIH has recognized the importance of RNAi and is investing in its development, delivery of RNAi to the nervous system presents special problems. For this reason, the NINDS will solicit proposals to develop methods for delivering RNAi therapeutically to the nervous system. The Institute is also continuing an ongoing solicitation to improve our understanding of neuroprotective barriers in health and disease and to develop methods to deliver therapies across them. The blood-brain barrier protects the brain and spinal cord from potentially harmful substances in the general circulation, but also restricts the entry of potentially therapeutic agents for many neurological disorders.

Non-human lend viral models of the neurological complications of AIDS: Cognitive impairment, movement problems, and disorders of the nerves of the body are common, and often devastating, complications of infection by the HIV virus. Developing treatments for these complications has been hampered because the HIV virus is narrowly targeted to humans, and animal models that mimic the human neurological problems are not available. Several closely related viruses, the lentiviruses, do infect other animals. In accordance with the NIH FY 2006 Plan for HJV-Related Research, the NINDS is therefore soliciting grant proposals to develop animal models that mimic the neurological complications of HIV infection.

CINAPS drug optimization program: In 2003, the NINDS established the Committee to Identify N euro protective Agents for Parkinson's (CINAPS). The CINAPS solicited candidate drugs to slow the progress of Parkinson's disease from scientists, pharmaceutical companies, and the lay public, and evaluated the drugs according lo a rigorous set of objective criteria. In all, 59 drug candidates, proposed by 42 scientists from 13 countries were evaluated. From these, 4 were selected and are now being tested in clinical trials though the NINDS Neuroprotection Exploratory Trials in Parkinson's Disease (NET-PD). This innovative drug selection process has been discussed widely and adopted by other disease communities, including Huntington's disease, ALS, and spinal muscular atrophy. For many potential drugs, there is insufficient preclinical data available to answer the questions needed to select drugs and design efficient clinical trials. To enhance the quality of preclinical information used for CINAPS selection and

for planning clinical trials, the NINDS will establish a contract facility to conduct the needed animal tests and provide research support for the CINAPS process.

Mechanisms of Transmission and Dissemination of Transmissible Spongiform Encephalopathies (TSEs): The transmissible spongifonn encephalopathies include Creutzfeldt-Jakob (CJD) disease in humans, bovine spongiform enccphalopathy (BSE, mad cow disease), and chronic wasting disease (CWD) in deer and elk. The link of BSE to a new variant of CJD in Europe and the spread of CWD in parts of the Western and Midwestern U.S. have increased the public health importance TSEs. NINDS research on TSEs, beginning in the 1950's, laid a scientific foundation for responding to the current public health concerns. Although BSE was spread largely through consumption of contaminated feed, and consumption of contaminated beef products has been linked to variant CJD, the mechanisms by which the TSE agent is spread and progresses within the body are poorly understood. As part of its continuing programs in TSE research, and in accordance with the Institute's role in the DHHS TSE/BSE Action Plan, the NJNDS will solicit research proposals focused on the mechanisms by which TSEs are transmitted.

Counterterrorism: Several chemical agents and toxins target the nervous system and could serve as terrorist weapons. The nervous system is also vulnerable to infectious agents that could be used in a terrorist attack. The NINDS works closely with the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) and with other DHHS components to identify high priority counterterrorism research issues that the NINDS is best qualified to pursue. High priority areas include persistent seizures, neuroprotection, and neurodegeneration. The greater diversity of the general public compared to the military in age and health status is also an important issue for the NINDS. In 2003, the NINDS initiated a program that supplements current grantees to expand ongoing research to issues relevant to counlerterrorism. In April 2004, the NINDS organized a scientific workshop that brought together experts in military research programs with scientists from the academic neuroscience community to help define priorities. The Institute is extending the supplement program and will solicit new grants on counterterrorism concerns relevant to the NINDS mission. The Institute continues to work with the National Institute of Allergy and Infectious Diseases (NIAID), which leads the NIH on counterterrorism issues, in planning for counterterrorism. The NINDS will solicit additional research proposals targeted to specific neurological counterterrorism issues as appropriate within the context of the NIH and DHHS planning efforts.

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. Recent workshops have focused on HIV/AIDS, multiple sclerosis, stroke, Parkinson's disease, tuberous sclerosis, neurofibromatosis, Batten disease, vascular cognitive impairment, stroke, fragile X syndrome, spinal muscular atrophy, and autism. Among the workshops now under development are meetings on vascular cognitive impairment, hydrocephalus, Down syndrome, non-epileptic seizures, and Parkinson's disease.

Other Areas of Interest

New initiatives are an important means by which the NINDS directs research toward its mission, but continuing programs constitute the major part of the Institute's activities. Most programs are designed to adapt to the changing scientific landscape by engaging the wisdom and ingenuity of the research community through investigator-initiated grant proposals. Comprehensive programs and grant mechanisms are tailored to translate basic research insights to therapies and to expedite clinical trials across the spectrum of neurological diseases. Stimulating collaboration among researchers is an important theme across all NINDS programs. Implementing the recommendations of disease focused planning efforts is another priority that transcends fiscal years and individual initiatives. The following highlights continuing NINDS programs:

Clinical research and clinical trials: The NINDS currently supports more than 1000 extramural and intramural research projects that involve human subjects. For example, epidemiological studies are examining risk factors for stroke with special attention to Blacks and Hispanics, genetic studies have recently helped identify genes related to Parkinson's disease, ALS, dystonia, Joubert syndrome, and cerebrovascular disease, and brain imaging research is investigating how the brain develops throughout childhood and how it adapts after damage. As one indication of the scope, more than 300,000 people are expected to participate over the course of currently funded clinical research studies.

Of these clinical research studies, approximately 125, with more than 25,000 expected participants, are clinical trials of interventions to prevent or treat neurological disorders. As for all N1H clinical trials, information is freely available to potential participants at http://clinicaltrials.gov. The NINDS often conducts trials on questions that are unlikely to be the focus of industry efforts. Current examples include trials of surgical treatment for epilepsy and of combination therapies for multiple sclerosis, and in past years pioneering NINDS trials developed the first acute treatment effective for stroke, as well as a continuing series of advances in stroke prevention. Studies range from planning, through pilot trials and early phase investigations, to large phase III multi-center projects. New or ongoing trials focus on a wide variety of disorders, including AIDS, ALS, brain tumor, Canavan disease, cerebral palsy, dystonia, epilepsy, essential tremor, Huntington's disease, migraine, multiple sclerosis, pain, Parkinson's disease, periodic paralysis, sickle cell disease, stroke and traumatic brain injury. Among interventions under study are drugs, surgery, gene transfer, deep brain stimulation, hypothermia, immunotherapy, vaccines, and behavioral therapy.

To facilitate clinical trials and manage them effectively, the NINDS has implemented grant mechanisms tailored 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 web-based "toolkit," of resources on design, implementation and oversight to help investigators develop clinical trials applications; supplemented clinical trials to collect DNA samples for the 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. The NINDS Pilot Studies Network, now underway, is designed to expedite pilot trials of new treatments for neurological disorders. The Clinical Research Collaboration (CRC),

now under development, 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. The Institute is also an active participant in the NIH Roadmap initiatives for "Re-engineering the Clinical Research Enterprise," which address issues that go beyond the mission of neurology alone, such as harmonizing requirements related to clinical research among government agencies.

Translational research: Translational research encompasses the many steps that move basic research findings to a therapy that is ready for testing in clinical trials. In 2002, the NINDS responded to the increasing opportunities arising from neuroscience research by developing a comprehensive translational research program that can apply to all diseases within its mission. The NINDS Cooperative Program in Translational Research and Exploratory/Developmental Projects in Translational Research solicit investigator-initiated proposals and evaluate them according to peer review criteria tailored to the needs of translational research. The grant mechanisms foster cooperative research. NINDS scientific staff and outside experts closely monitor progress with milestone-driven funding, as is common in industry. For example, the first major project in this program, the Parkinson's Gene Therapy Study Group, met critical milestones this year with the creation of a stable colony of parkinsonian non-human primates and the development of modified viral vectors that can deliver therapeutic genes under tight control. Other ongoing projects in this program are investigating drug, stem cell, or gene therapy for ALS, brain tumor, epilepsy, Huntington's disease, Parkinson's disease, tuberous sclerosis, traumatic brain injury, stroke, or other disorders. In 2004, the Institute reissued the program announcements for the program, with increased efforts to engage small businesses through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grant programs. Complementing the broad translational research program are several specific NINDS efforts. Among these:

Anticonvulsant screening project: The NINDS Anticonvulsant Screening Project (ASP) catalyzes academic and industry efforts to develop drugs for epilepsy by screening candidate drugs in a series of standardized cell culture and animal models. Since 1975, the ASP has screened more than 25,000 drugs from more than 400 academic and industry partners in 31 countries. Several of these drugs are now in clinical use, and others are currently in clinical development. Guided by the Epilepsy Benchmarks planning process, the ASP is increasing efforts on drugs to prevent the development of epilepsy and for treatment-resistant epilepsy. The ASP is also developing a database of its rich repository of information relating the activity of drugs to their chemical structure. This resource will be available to all researchers and the public.

SMA Project: The Spinal Muscular Atrophy (SMA) Project is a program to develop therapies for SMA. In recent years, scientists discovered the gene defects that cause SMA, developed animal models that mimic the human disease, and devised plausible strategies for developing therapies. Because of the impact of SMA on children and families and the state of the science, the NINDS chose SMA as the focus of an innovative approach to expedite the therapy development. The performance-based contract mechanism accelerates all steps from recognition of a research need, through solicitation, review, and funding of targeted research subprojects. An expert steering committee, with members from academia, industry, the FDA and the NIH, actively drives the

process. Ill its first year, the SMA Project has moved quickly. The steering committee developed detailed plans for SMA drug development, and planning for gene therapy is underway. The SMA project issued 6 solicitations for targeted research subprojects, and research has begun. Following the rigorous CINAPS approach that the NINDS devised to evaluate potential drugs for Parkinson's disease, the Institute has solicited suggestions for existing drugs that might be ready for testing against SMA in clinical trials. A workshop in September 2004 engaged the SMA scientific community, clinicians, and voluntary health organizations on development of clinical trials. As the SMA Project proceeds, the NINDS is evaluating whether this approach might be applied to other disorders. Details of the SMA Project are available to scientists and the community through at: http://www.smaproject.org/.

Other drug development programs: The NINDS is continuing several other drug development programs for neurological disorders. In 2002, the Institute, working with academia and voluntary disease organizations, fonned a consortium of 26 laboratories to screen a set of 1040 known drugs with laboratory tests for potential use against neurodegenerative diseases. Most of the drugs in this set have been approved by the U.S. Food and Drug Administration (FDA) for other uses, and so might move more quickly toward clinical trials. The Institute has since provided supplemental funding for follow up testing of drugs that emerged from this process in more definitive mouse models of human neurodegeneration. One drug, ceftriaxone, has already proceeded to testing in a clinical trial for ALS. Another NINDS drug development supplement program aims to overcome barriers to therapeutics development for stroke, brain tumor, SMA, Alzheimer's disease, polyglutamine diseases (a group of inherited disorders), cerebral arteriovenous malformations, and other diseases. The Institute continues to supports the NINDS High Throughput Drug Screening Service Facility and the development of appropriate neurological disease oriented assays (tests). High throughput screening uses robotics and miniaturized assays to rapidly test large numbers of chemicals to find lead compounds for use in drug development and as research tools. At the trans-NIH level, the Institute is active in programs that complement NINDS drug development efforts; the Brain Institutes Bioactive Compound Library and the NIH Roadmap Molecular Libraries initiatives are creating chemical databases, molecular compound libraries, assays, screening centers, and other resources.

Minority health: Led by the NINDS Office of Minority Health and Research (OMHR), the Institute encourages the training and development of minority research and health professionals and develops and implements plans to address health disparities. The continuing Specialized Neuroscience Research Program (SNRP) has been notably successful, as evident from published research, success in competing for independent NIH research grants, and fostering of new neuroscience departments and divisions. Seven other NIH components have joined NINDS in supporting this program. The OMHR led the development of the NINDS Five-Year Strategic Plan on Minority Health Disparities, with its increased focus on diseases such as stroke, AIDS, and epilepsy. The NINDS also leads the NIH in pursuing a Government Performance and Results Act (GPRA) goal to identify culturally appropriate, effective stroke prevention programs for nation-wide implementation in minority communities by FY 2010. The Institute supports many relevant clinical studies, clinical trials, and epidemiological investigations, but expanded activities will be necessary to accomplish this goal. Finally, the NINDS is an active participant in the DHHS Stroke Belt Elimination Initiative (SBEI) through expansion of the ongoing NINDS

REGARDS study (Reasons for Geographic and Racial Differences in Stroke), which is determining stroke risk in a national sample of 30,000 white and African-American subjects.

Centers, collaborative efforts, and common resources: Because neuroscience is inherently muiti-disciplinary, team research and common resources are essential. The NINDS provides for this need through support for investigator-initiated, multi-investigator grants and Center Core Grants (P30's), through supplements that address issues such as sharing of mouse models, and in specific programs. These programs include 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 NINDS High Throughput Drug Screening Service Facility, the NINDS/NIMH Microarray Consortium, and the NINDS Human Genetics Repository. The Institute currently supports centers focused on particular disorders including Parkinson's disease, traumatic brain injury, pain, brain tumor, autism, neonatal brain injury, epilepsy, Huntington's disease, multiple sclerosis, and muscular dystrophy. The NINDS also has joined efforts with the National Science Foundation in cooperative research on computational neuroscience and informatics research. Examples of ongoing NINDS programs include:

Center core grants: In 2002, the MMDS began a program to provide shared research resources to groups of NINDS grantees. These Center Core Grants foster an interactive research environment and stimulate multi-discipHnary approaches to neuroscience problems. The grants support basic, translational, or clinical research. Cores supported to date include resources for specialized light and electron microscopy, animal models of human disorders, informatics and statistics, proteomics, DNA sequencing, and brain imaging.

NINDS/NIMH Microarray Consortium: Gene microarrays allow scientists to simultaneously monitor the activity of virtually all genes in the brain, with wide potential applications to basic and clinical neuroscience. Studies of gene expression (activity) may, for example, give crucial clues about what goes wrong in the brain during disease and help predict which patients will respond to available therapies. In fiscal year 2002, the NINDS, with NIMH participation, established three microarray centers for study of gene expression in the nervous system. These centers function as a consortium, providing reagents, services, technology development, and training to the neuroscience community. The consortium has already completed more than 50 projects, with as many in progress. These relate to diseases including Alzheimer's, autism, brain tumor, epilepsy, Huntington's, spinoccrebellar ataxia and stroke, and to basic science areas including stem cells, brain plasticity, and regeneration. The consortium provides data from all studies and analysis tools to the public on their website (http://aiTayconsortium.tgen.org/).

NINDS Human Genetics Repository: To support research on genetic factors in neurological disorders, in 2003 the NINDS established a repository that collects, stores, characterizes and distributes DNA samples and cell lines for the research community. The repository currently has material relating to stroke, epilepsy, Parkinson's disease, and motor neuron diseases, including ALS. The growth has been encouraging, with more than 4700 samples from more than 2500 unique individuals included within less than a year after the repository was established, and an increasing range of ethnic and geographic diversity. The Institute has developed a program of supplements for ongoing NINDS clinical trials to collect genetic material from patients.

Implementation of disease-specific planning efforts: Major NINDS disease-focused planning efforts include the Parkinson's Disease Research Agenda and Matrix; the Epilepsy Benchmarks; the Brain Tumor and the Stroke Progress Review Groups (PRGs); and the Five-Year Strategic Plan on Minority Health Disparities. In the past year, the NINDS also led the development of research goals for tuberous sclerosis complex (TSC), the Muscular Dystrophy Coordinating Committee developed the research and education plan for NIH required by the MD-Care Act, and the Interagency Autism Coordinating Committee developed a research planning matrix for autism, hi addition, the Institute attends to Institute of Medicine reports on multiple sclerosis, autism, transmissible spongiform encephalopathies and other research issues. Finally, the NINDS receives guidance from several scientific workshops each year that assess the state of the science for research specific disorders. Recent examples include lipid storage disorders, neurofibromatosis, and Batten disease. The NINDS is implementing recommendations from these planning efforts, which together engaged hundreds of scientists from government, academia, and industry, as well as representatives of voluntary health organizations. Reports on several of these planning and implementation efforts are available on the NINDS website at: http://www.ninds.nih.gov/about_ninds/ninds_plans.htm. The following illustrate ongoing implementation efforts, in addition to new initiatives already described for FY 2006:

Brain tumor: The NINDS and the National Cancer Institute (NCI) jointly established the Brain Tumor Progress Review Group (BT-PRG) to identify and prioritize unmet scientific needs and opportunities that are critical to the advancement of brain tumor research. The Brain Tumor Genome Anatomy Project (BTGAP) f the Specialized Programs of Research Excellence (SPORES), and an enhanced intramural program in neurooncology represent collaborative efforts with the NCI. Recent NINDS-led initiatives on neuroprotective barriers in central nervous system diseases (PAS-03-165), on gene therapy for neurological disorders (RFA-NS-02-007), and on understanding and preventing brain tumor dispersal (PAS-04-079) also address priorities identified by the BT-PRG.

Stroke: In 2001, the NINDS convened a meeting of 150 nationally and internationally recognized stroke experts, called the Stroke Progress Review Group (PRG) Roundtable, to identify gaps in stroke knowledge and set research priorities. In January 2003, the NINDS met again with the PRG to discuss activities to date and future directions, and a March 2004 Stroke PRG Implementation Report, available on the NINDS website, lists dozens of programs, initiatives, and workshops that respond to priorities identified in the original PRG report. In the past year, the Institute has expanded the network of SPOTRIAS (Specialized Program of Translationai Research in Acute Stroke) centers, which facilitate translation of basic research findings into clinical practice. Other activities include: the NINDS Human Genetic Resource Center, which provides DNA and cell lines for study of stroke genetics; solicitations on "Neuroprotective Barriers in Neurological Diseases," (PAS-03-165), "Reducing Stroke Disparities Through Risk Factor Self-Management," (PAS-03-166), "Neurovascular Mechanisms of Brain Function and Disease," (PAS-04-072), "Genetics and pathobiology of Vascular Cognitive Impairment" (PAS-04-149), and "Novel Targets and Therapy Development for Stroke" (RFA-HL-05-004). In addition, the NINDS has convened scientific workshops focused on racial and ethnic disparities in stroke, improving access to treatments for stroke patients, priorities for clinical research on treatment of hemorrhagic (bleeding) stroke, genetics of vascular cognitive impairment, and on stroke risk assessment and primary prevention. The NINDS Intramural stroke program also

conducts pioneering research on stroke, including vaccine approaches to stroke prevention, brain imaging for stroke diagnosis, and novel emergency stroke therapies. Stroke centers at Suburban Hospital in Bethesda, Maryland and Washington Hospital Center, in the District of Columbia, are an important aspect of these efforts. The NINDS and NHLBI have formed an active working group focused on stroke research, and many of the items listed here are cooperative efforts with the NHLBI. The Institute also works closely with voluntary health organizations and professional groups through the Brain Attack Coalition and other efforts.

Parkinson 's disease: Since the inception of the NIH Parkinson's Disease Research Agenda in 2000, the NTNDS has led an unprecedented implementation effort, with significant progress. As part of the Agenda implementation process, the NIH engages scientists from the research community in periodic reviews of progress and recommendations for future action. Following a Summit meeting that the NIH Director convened in 2002 with an outstanding group of scientists, the NINDS developed a Matrix of action items that address roadblocks to progress, arrayed according to short-to-long time range, and low-to-high risk of accomplishment. The Matrix is revised and expanded as goals are achieved and new goals are identified. For the summer of 2005, the NINDS is again planning a Parkinson's Disease Research Summit to assess the state of the science, identify scientific opportunities, discuss potential roadblocks to progress, and develop a plan for future action. The Parkinson's Disease Coordinating Committee coordinates research across NIH, and with the Parkinson's disease research programs in the Department of Veterans Affairs and the Department of Defense. The NIH also works closely with private organizations on initiatives, scientific meetings, and special projects. Parkinson's disease will remain a high priority of the institute until die goal of preventing or curing the disease is reached.

In response to the Agenda and Matrix, the NIH has initiated extensive programs to develop drug therapies for Parkinson's disease, to refine and expand surgical interventions including deep brain stimulation, to move gene therapy closer to the clinic, and to explore cell transplantation therapies. These efforts include, for example, the Deep Brain Stimulation (DBS) Consortium and a major clinical trial of DBS in cooperation with the Department of Veterans Affairs, the Parkinson's Disease Gene Therapy Study Group, translational research projects in stem cells for Parkinson's disease, high throughput drug screening, and the Neuroprotection Exploratory Trials in Parkinson's disease (NET-PD), which is a program of clinical trials of drugs to slow the progression of Parkinson's disease. Through investigator initiated research and targeted initiatives, the NIH is also funding more projects than ever before to better understand what triggers Parkinson's disease and how it progresses and to understand and treat non-motor symptoms of the disease. The Morris K. Udall Parkinson's Disease Research Centers of Excellence are an integral part of these efforts, and the NINDS has expanded the clinical activities of these centers. Extensive details of the full range of NIH Parkinson's disease activities are available on the Parkinson's Disease Research Web at: lrttp://www.iunds.nih.gov/parkinsonsweb/index.htm.

Epilepsy: In March 2000, the NINDS organized the conference "Curing Epilepsy: Focus on the Future" in cooperation with several patient advocacy groups. The meeting initiated a planning process that identified seventeen specific research "benchmarks" for the epilepsy research community to measure progress towards finding a cure for epilepsy. The NINDS Epilepsy Research Web (h_rjL//www.ninds_J ih.gov/epilepsyweb) describes the benchmarks and ongoing

research to accomplish them, including several targeted scientific workshops and initiatives. The expansion of efforts in the NINDS Anticonvulsant Screening Project to find better drugs for treatment resistant epilepsy and to prevent the development of epilepsy is one important aspect of these efforts. Other activities include collection of DNA samples to facilitate study of genes in epilepsy, microarray studies of gene expression, the development of better animal models of epilepsy development and treatment resistant epilepsy, and major clinical trials on issues including surgical interventions and treatment of childhood absence epilepsy.

Muscular dystrophy: In accordance with the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84), the Secretary of DHHS established the Muscular Dystrophy Coordinating Committee, which developed an NIH research and education plan for the muscular dystrophies. The NINDS, the National Institute of Child Health and Human Development and the National Institute of Arthritis and Musculoskeletai and Skin Diseases (NIAMS), are committed to pursing the goals of that plan. Priorities include understanding the mechanisms of disease; improving diagnosis and screening; pursuing treatment strategies; addressing rehabilitation, quality of life, and psychosocial issues; and meeting research infrastructure and training needs. The Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers play a central role in these efforts, with 3 centers funded so far and solicitations issued in 2004 to fund additional centers. Also in keeping with the goals of plan, the NINDS, NICHD and NIAMS are soliciting grant proposals on understanding the disease process and on approaches for treatment, and a series of three initiatives underway to increase the number of investigators in muscular dystrophy research.

Multiple sclerosis: People who have multiple sclerosis are better off now than a decade ago because of therapies that reduce symptoms and slow the progression of disease. The NIH supported basic and clinical research that contributed to the development of currently available therapies, as well as research on interventions that are now in clinical testing phases. The NINDS, working with other components of the NIH, is continuing its longstanding commitment to basic, translational, and clinical research on multiple sclerosis. Recent workshops have focused on critical issues that include genetics of multiple sclerosis and finding biomarkers (measurable indicators) that will aid diagnosis, predict disease course, and expedite testing of new therapies. The NINDS has added a large biomarker study to an ongoing clinical trial and solicited grant proposals on biomarkers and on axon (nerve fiber) damage in multiple sclerosis. Ongoing clinical trials include a major test of whether combining two available therapies for multiple sclerosis is superior to either alone. The NINDS intramural program also continues to be a leader in many aspects of multiple sclerosis research.

Pain: As the largest NIH supporter of research on pain, the NINDS is one of the leaders of the NIH Pain Consortium. The consortium was established to enhance pain research and to promote collaboration among the many NIH Institutes and Centers that have activities addressing pain. Following a thorough review of all NIH pain related activities during the past year, the Consortium is developing a comprehensive NIH pain research agenda that will include research on mechanisms of pain, ways to translate from basic research to pain management, strategies for introducing findings into practice, development of novel pain therapies and pain epidemiology. Recent workshops have focused *on* complex regional pain syndrome/reflex sympathetic dystrophy and on TMJ disorders. Ongoing initiatives include "Neurobiotogy of Persistent Pain

Mediated by the Trigeminal Nerve" (PAS-03-173), "Biobehavioral Pain Research" (PA-03-152), and "Neurobiology of Complex Regional Pain Syndrome/Reflex Sympathetic Dystrophy" (PAS-03-120). Information about pain and Consortium activities is available for physicians, researchers, and the public at: http://painconsortium.nih.gov.

Other: The NINDS is pursuing disease specific goals relevant to several other disorders. Among recent and ongoing initiatives not mentioned elsewhere are initiatives that focus on gene discovery in autism, studies on the causes and mechanisms of dystonia, therapeutic opportunities in progressive stages of spinal cord injury, therapies for lysosomal storage disorders, centers for neurofibromatosis, and HIV in the central nervous system.

Training: Training basic and clinical neuroscientists is integral to the mission of the NINDS. In addition to support for extramural trainees through research grants, the Institute supports pre- and postdoctoral students through individual and institutional training programs, and basic and clinical scientists through early and mid-career development awards, including programs to encourage minority participation. The NINDS Intramural program offers opportunities for talented high-school, undergraduate, graduate and medical students, as well as more advanced training. The NINDS also participates in the NIH Loan Repayment Program, which encourages health professionals to undertake clinical and pediatric research.

International programs: In 2004, the NINDS created the Office of International Activities to promote international research, training, and collaborations that are relevant to the institute's mission. Among other activities for fiscal year 2006, the Institute is working with the NIH Fogarty International Center to addresses brain disorders in middle and low income countries through collaborations with U.S. scientists.

Public Information: The NINDS is a source of reliable information about neurological disorders for the public, the press, and professional organizations. The Institute provides fact sheets about hundreds of neurological disorders, news in neuroscience, and descriptions of NINDS activities, including funding opportunities, on its heavily used website (http://www.nind5.nih.gov/). The site also presents links to helpful resources including voluntary health organizations relevant to particular diseases and information for people seeking to participate in clinical trials. In addition, the Office of Communications and Public Liaison prepares and distributes public information documents in English and Spanish, and responds to thousands of requests for information about neurological disorders by web, phone, email, or letter from the public and the press. The Institute works closely with more than 300 professional and voluntary health organizations focused on neurological disorders, with frequent interactions and coordinated activities that include joint scientific workshops and grant solicitations.

Since the middle of the 1990s, the NINDS has actively promoted understanding of the serious public health issues related to stroke, through billboards, public service radio and television advertising, a community education kit with a consumer education video, posters, brochures in English and Spanish, strategic partnerships with interested organizations, media outreach, faith-based media events, a traveling exhibit, and online public service marketing. The campaign has included professional education and minority outreach, including a training DVD in partnership with the American Stroke Association, the American Academy of Neurology, and the National

Stroke Association, and a joint initiative with the U.S. Centers for Disease Control and Prevention (CDC) through their state health programs. The NINDS chairs the Brain Attack Coalition. The mission of this group of professional, voluntary and government organizations is to reduce the occurrence, disabilities and death associated with stroke.

The_NIH_Neuroscience Blueprint

Overview -- The Blueprint is a framework to enhance cooperation among fifteen NIH Institutes and Centers that support research on the nervous system. Over the past decade, driven by the science, the NIH neuroscience Institutes and Centers have increasingly joined forces through initiatives and working groups focused on specific disorders. The Blueprint builds on this foundation, making collaboration a day-to-day part of how the NIH does business in neuroscience. By pooling resources and expertise, the Blueprint can take advantage of economies of scale, confront challenges too large for any single Institute, and develop research tools and infrastructure that will serve the entire neuroscience community.

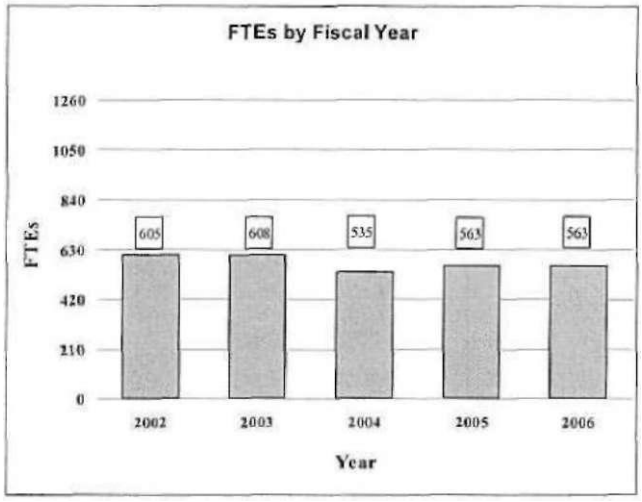
FY2005 — For Fiscal year 2005, the Blueprint participants are developing an initial set of initiatives focused on tools, resources, and training that can have a quick and substantial impact because each builds on existing programs. These initiatives, with the participation of all Blueprint Institutes, include an inventory and analysis of neuroscience tools funded by the NIH and other government agencies, enhancement of training in the neurobioiogy of disease for basic neuroscientists, and expansion of ongoing gene expression database efforts. The NINDS will coordinate an expansion of the ongoing Gene Expression Nervous System Atlas, or GENSAT, project to include the eye, ear, and other parts of the nervous system, as well as the brain. GENSAT is designed to help answer a wide range of questions about how the brain develops, works, and goes wrong in disease by mapping the activity of thousands of genes in the brain. GENSAT also provides genetically engineered mouse strains that that allow scientists to classify, observe, and track brain cell types according to molecular characteristics and function. The GENSAT project is showing substantial progress and data are made publicly available through the NIH's National Center for Biotechnology Information (NCBI), and thereby constitute an unprecedented resource for neuroscience research.

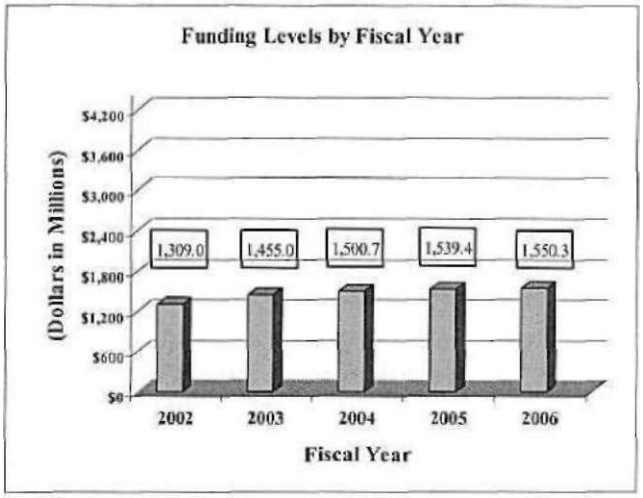
• **FY2006** — Advances in the neurosciences and the emergence of powerful new technologies offer many opportunities for Blueprint activities that will enhance the effectiveness and efficiency of neuroscience research. Blueprint initiatives for fiscal year 2006 will include systematic development of genetically engineered mouse strains of critical importance to research on nervous system and its diseases and training in critical cross cutting areas such as neuroimaging and computational biology. The NINDS will coordinate with the other Blueprint Institutes an initiative to provide specialized neuroscience resources, or "cores." Cores might include equipment, facilities, and technical support for animal models, cell culture, computer modeling, DNA sequencing, drug screening, gene vectors, imaging, mass spectrometry, microarrays, microscopy, molecular biology, proteomics or other common needs that arise. Existing core facility grants promote interdisciplinary collaboration and cooperation among scientists who use them. The Blueprint **will** increase efficiency and broaden the impact of core programs by serving laboratories from many NIH Institutes and Centers, rather than a single Institute.

Budget Policy

The Fiscal Year 2006 budget request for the NINDS is $1,550,260,000, an increase of $10,812,000 and 0.7 percent over the FY 2005 Appropriation. Also included in the FY 2006 request is NINDS's support for the trans-NIH Roadmap initiatives, estimated at 0.89% of the FY 2006 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.





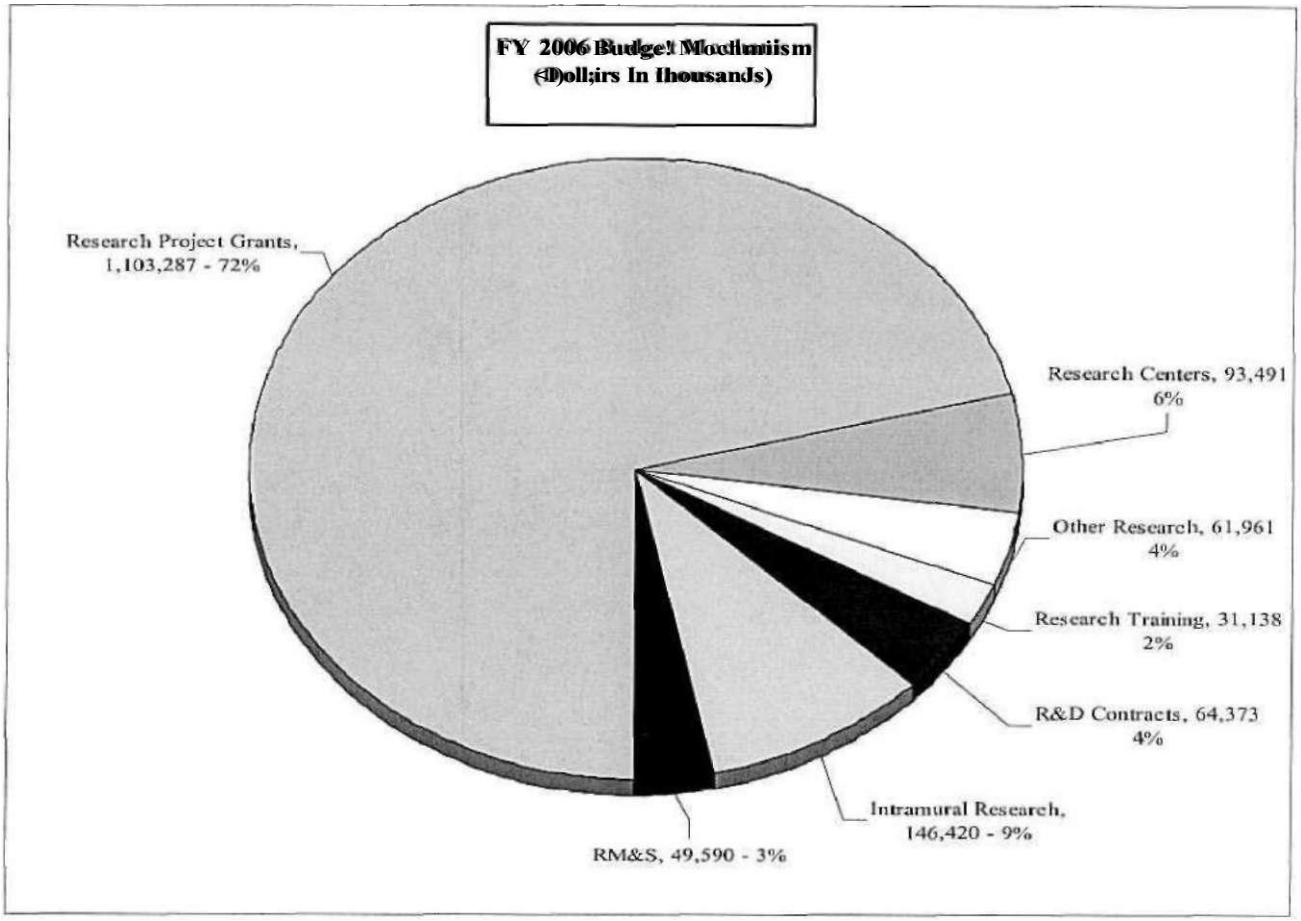
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. The average cost of competing RPGs will be held at the FY2005 level. There will be no inflationary increases for direct, recurring costs in Noncompeting continuation RPGs.

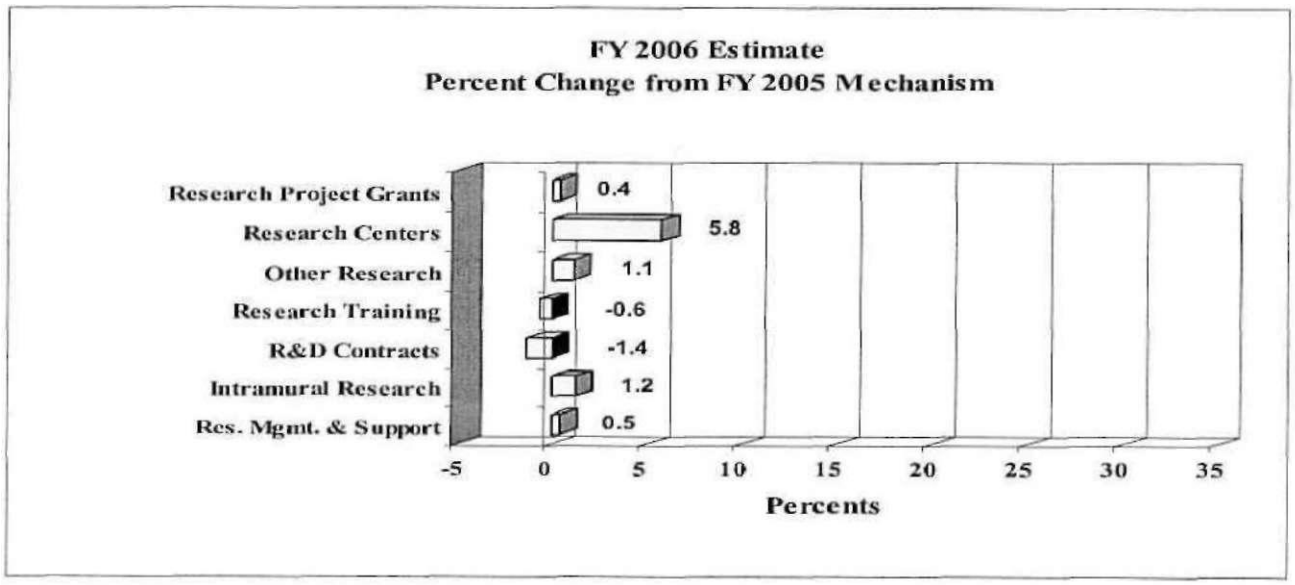
Advancement in medical research is dependent on attracting the best and the brightest to pursue careers in biomedical research. In the Fiscal Year 2006 request, stipend levels for post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will increase by 4.0% for those with 1-2 years of experience, with all other stipends remaining at the FY2005 levels. NIH will also provide an increase of S500 per post-doctoral fellow, for increased health insurance costs. This increase in stipends and health benefits is financed within the FY2006 request by reducing the number of Full-Time Training Positions by 10. NINDS will support 784 pre- and postdoctoral trainees in full-time training positions.

The Fiscal Year 2006 request includes funding for 71 research centers, 412 other research grants, including 284 clinical career awards, and 150 R&D contracts. Intramural Research and Research Management and Support receive increases of 12 percent and 0.5 percent respectively.

NINDS is participating in the NIH Neuroscience Blueprint. The FY2006 request includes $7.8 million for a variety of Neuroscience Blueprint initiatives, including neuroscience cores, training initiatives, and the Neuromouse project.

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





Budge! Mechanism • Total

MECHANISM	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncoinpctitlg	2,029	5766,820,000	1,986	S820.724.00O	2,036	5821,280,000
Administrative supplements	(159)	12,910,000	(201)	12,219,000	(200)	12,000,000
Competing:						
i Renewal	254	102,743,000	221	89,469,000	224	90,820,000
New	492	160,897,000	428	140,109,000	435	142,225,000
Supplements	*1*	470,000	2	409,000	2	415,000
Subtotal, competing	748	2(34,110,000	651	229,987,000	661	233,460,000
Subtotal, RPCs	2,777	1,043,840,000	2,637	1,062,930,000	2,(597	1,066,740,000
SBIK/STTR	12S	35,902,000	125	36.28S.0OO	126	36,547,000
Subtotal, RPGs	2,905	1,079,742,000	2,762	1,099,218,000	2,323	1,103,287,000
Research Centers:						
Specialized/comprehensive	61	74,009,000	66	87,408,000	69	92,128,000
Clinical research	0	0	0	0	0	0
Biotechnology	I	626,000	1	980,000	2	1,363,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	62	74,635,000	67	88,388,000	71	93,491,000
Other Research:						
Research careers	246	37,637,000	280	42,309,000	284	42,921,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	7	2,082,000	77	7,800,000	77	7,800,000
Biomedieal research support	0	28,000	0	36,000	0	42,000
Minority biomedical research support	6	1,885,000	6	l,S92,O00	6	1,892,000
Other	55	9,738,000	45	9,223,000	45	9,306,000
Subtotal, Other Research	314	51,370,000	408	61,260,000	412	61,961,000
Total Research Grants	3,281	1,205,747,000	3,237	1,248,866,000	3,306	1,258,739,000
Rcscarcii Traininp:	FTTPs		FTTPs		FiTPs	
individual awards	365	13,653,000	372	14,034,000	365	14,034,000
Institutional awards	413	16,821,000	422	17,304,000	419	17,104,000
Total, Training	778	30,474,000	794	31,338,000	784	31,138,000
Rcscarcii & development contracts	152	80,166,000	150	65,256,000	150	64,373,000
(SBIR/STTR)	**0)**	(554,000)	**(0**	(500,000)	(1)	(500,000)
	FTEs		FTEs		FTEs	
Intramural research	392	138,016,000	400	144,621,000	400	146,420,000
Research management and support	143	46,290,000	163	49,367,000	163	49,590,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
Total, N'INDS	535	1,500,693,000	563	1,539,448,000	563	1,550,260,000
'Road Map Support)		(5,156,000)		(9,652,000)		(13,863,000)
Clinical Trials)		(98,964,000)		(101,320,000)		(101,693,000)

Budget Authority hv Activity
(dollars in thousands)

ACTIVITY	FY 2004 Actual		FY 2005 Appropriation		**FY** 2006 Estimate		Change	
	FTEs	Amount	FTEs	A mo Lint	FTEs	Amount	FTEs	Amount
Extramural Research		SI, 516,387		SI,345,460		51,354,250		S8,790
Intramural research	392	**138,016**	400	144,621	400	146,420	0	\.*i99*
Res. management & support	143	46,290	163	49,367	163	49,590	t)	223
Cancer Control & Prevention	0	0	0	0	0	0	0	0
Total	535	1,509,693	563	1,539,448	563	1,550,260	0	10,812

Summary of Changes

FY 2005 Appropriation				51,539,448,000
FY 2006 Estimated Budget Authority				1,550,260,000
Net change				10,812,000
	FY 2005 Appropriaton		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. **Within** grade increase		$47,594,000		$719,000
b. Annual ization of January 2005 pay increase		47,594,000		440,000
c. January 2006 pay increase		47,594,000		821,000
d. One less day of pay		47,594,000		(182,000)
e. Payment for centrally furnished services		23,626,000		12,000
f. Increased cost of laboratory supplies, materials, and other expenses		73,401,000		839,000
Subtotal				2,649,000
2. Research Management and Support:				
a. Within grade increase		18,208,000		317,000
b. Annualization of January 2005 pay increase		18,208,000		168,000
c. January 2006 pay increase		18,208,000		314,000
d. One less day of pay		18,208,000		(70,000)
e. Payment for centrally furnished services		10,699,000		5,000
f. Increased cost of laboratory supplies, materials, and other expenses		20,460,000		238,000
Subtotal				972,000
Subtotal, Built-in				3,621,000

Summary of Changes—continued

CHANGES	2005 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	1,986	$832,943,000	50	$337,000
b. Competing	651	229,987,000	10	3,473,000
c. SB1R/STTR	125	36,288,000	1	259,000
Total	2,762	1,099,218,000	61	4,069,000
2. Research centers	67	88,388,000	4	5,103,000
3. Other research	408	61,260,000	4	701,000
4. Research training	794	31,338,000	(10)	(200,000)
5. Research and development contracts	150	65,256,000	150	(883,000)
Subtotal, extramural				8,790,000
	FTEs		FTEs	
6. Intramural research	400	144,621,000	0	(850,000)
7. Research management and support	163	49,367,000	0	(749,000)
8. Cancer control and prevention	0	0	0	0
9. Construction		0		0
10. Building and Facilities		0		0
Subtotal, program		1 ,539,448,000		7,191,000
Total changes	563		0	10,812,000

Budget Authority hy Object

	FY2OO5 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensablc workyears:			
Full-time employment	563	563	0
Full-time equivalent of overtime & holiday hours	1	1	0
Average OS salary	$0	$0	SO
Average GM/GS grade	11.3	11.4	0.1
Average GM/GS salary	$74,293,068	S76,263,692	$1,970,624
Average salary, grade established by act of July 1,1944{42U.S.C. 207)	SO	SO	$0
Average salary of ungraded positions	0	0	0

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
11,1 Full-Time Permanent	$26,975,000	527,713,000	$738,000
11.3 Other than Full-Time Permanent	18,832,000	19,331,000	499,000
11.5 Oilier Personnel Compensation	1,082,000	1,112,000	30,000
11.7 Military Personnel	715,000	734,000	ly.ooo
11.8 Special Personnel Services Payments	5,895,000	6,050,000	155,000
Tut.il, Personnel Compensation	53,499,000	54,940,000	1,441,000 |
12.0 Personnel Benefits	11,764,000	12,080,000	316,000
12.1 Military Personnel Benefits	539,000	553,000	14,000
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	65,802,000	67,573,000	1,771,000
21.0 Travel & Trans portalion o f Pc rs ons	3,380,000	3,447,000	67,000
22.0 Transportation oi'Things	201,000	205,000	4,000
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	73,000	74,000	1,000
23.3 Communications, Utilities & Miscellaneous Charges	976,000	996,000	20,000
24.0 Printing & Reproduction	758,000	773,000	15,000
25.1 Consulting Services	3,839,000	3,850,000	11,000
252 Other Services	12,064,000	12,195,000	131,000
25.3 Purchase of Goods & Services from Government Accounts	117,966,000	117,294,000	(672,000)
25.4 Operation & Maintenance of Facilities	3,171,000	3,234,000	63,000
25.5 Research & Development Contracts	22,515,000	21,890,000	(625,000)
25.6 Medical Care	1,305,000	1,331,000	26,000
25.7 Operation & Maintenance of Equipment	7,440,000	7,466,000	26,000
25.S Subsistence & Support cf Persons	0	0	0
25.0 Subtotal, Other Contractual Services	] 68,300,000	167,260,000	(1,040,000)
26.0 Supplies & Materials	9,709,000	9,862,000	153,000
31.0 Equipment	10,045,000	10,193,000	148,000
32.0 J ancl and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	1,280,204,000	1,289,877,000	9,673,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	0	0	0
44,0 Refunds	0	0	0
Subtotal, Non-Pay Costs	1,473,646,000	1,482,687,000	9,041,000
Total **Budget Authority** by Object	1,539,448,000	1,550,2<>0,000	10,812,000

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent **(11.1)**	$26,975,000	527,713,000	$738,000
Other Than **Full-Time** Permanent (11.3}	18,832,000	19,331,000	499,000
Other Personnel Compensation (11.5)	1,082,000	1,112,000	30,000
Military Personnel (11.7)	715,000	734,000	19,000
Special Personnel Services Payments (11.8)	5,895,000	6,050,000	155,000
Total Personnel Compensation (11.9)	53,499,000	54,940,000	**1,441,000**
Civilian Personnel Benefits (12.1)	11,764,000	12,080,000	316,000
Military Personnel Benefits (12.2)	539,000	553,000	
Benefits to Former Personnel **(1**3.0)	0	0	0
Subtotal, Pay Costs	65,802,000	67,573,000	**1,771,000**
Travel (21.0)	3,380,000	3,447,000	67,000
Transportation of Things (22.0)	201,000	205,000	4,000
Rental Payments to Others (23.2)	73,000	74,000	1,000
Communications, Utilities and Miscellaneous Charges (23.3)	976,000	996,000	20,000
Printing and Reproduction (24.0)	758,000	773,000	15,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	822,000	833,000	11,000
Other Services (25.2)	12,064,000	12,195,000	131,000
Purchases from Govt. Accounts (25.3)	71,101,000	70,371,000	(730,000)
Operation & Maintenance ofFacilities (25.4)	3,171,000	3,234,000	63,000
Operation & Maintenance of Equipment (25.7)	7,440,000	7,466,000	26,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	94,598,000	94,099,000	(499,000)
Supplies and Materials (26.0)	9,645,000	9,797,000	152,000
Subtotal, Non-Pay Costs	109,631,000	109,391,000	(240,000)
Total, Administrative Costs	**175,433,000**	**176,964,000**	**1,531,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

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

FY 20Q6 House Appropriations Committee Report Language (H. Rpt. 108-636)

Item

Epilepsy - Epilepsy remains a **major,** unsolved public health problem affecting the lives of millions of Americans and their families. The Committee seeks intensified efforts by the Institute to produce breakthroughs in the prevention, treatment, and eventual cure of epilepsy. The Committee applauds the development of benchmarks for epilepsy research resulting from the 'Curing Epilepsy: Focus on the Future' conference held in March 2000 and encourages the Institute to address important research issues raised at the "Living Well with Epilepsy IF conference held in July 2003. The Committee encourages NINDS to develop specific research plans and goals for the anti-epileptic drug development program. The Committee requests the Institute for an update on its plans to advance these areas of research at the fiscal year 2006 appropriations hearing, (p. 78)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is committed to understanding the causes of epilepsy and developing effective therapies for all forms of the disease, including those that affect children, the elderly, and individuals with intractable epilepsy. The ultimate goal of this research is to find a cure for epilepsy.

The "Benchmarks for Epilepsy Research" is a collaborative strategy for advancing progress in understanding the causes of epilepsy, preventing seizures in those at risk, and developing treatments without side effects. The NINDS continues to make progress in implementing the Benchmarks. For example, several Benchmarks focus on creating better animal models with which to study the development of epilepsy, to test potential therapies against intractable epilepsy, and to study the unique features and long-term consequences of pediatric forms of the disorder. In August 2003, NINDS issued a Request for Applications on "Model Validation for Antiepileptogenic and Resistant Epilepsy Therapies." Six projects have been awarded through this initiative. In May 2004, NINDS held a workshop to discuss strategies to develop more useful models to study pediatric epilepsy, particularly catastrophic epilepsy and intractable partial epilepsy. Outcomes from this meeting will be presented at the American Epilepsy Society annual meeting and published in a prominent epilepsy journal so that they are widely disseminated to the research community.

The CDC-sponsored Living Well with Epilepsy II conference highlighted the importance of reducing the stigma associated with a diagnosis of epilepsy, and identifying and reducing health

disparities. To begin to address issues of stigma in the developing world, the NINDS recently participated with the Fogariy **International** Center and several other NIH Institutes in two Requests for Applications ("Stigma and Global Health Research Program" and "Brain Disorders in the Developing World.") Through these initiatives, NINDS is currently funding projects to develop culturally appropriate programs to decrease the burden of epilepsy-related stigma in sub-Saharan Africa, China and Vietnam. The NINDS has also taken steps to address health disparities in epilepsy. In November 2002, the Institute hosted a planning panel meeting to develop a research agenda to identify and address disparities in epilepsy. As a result of this meeting, in August 2003, NINDS issued a Program Announcement on "Reducing Disparities in the Treatment of Epilepsy."

A long-standing and highly successful translational component of the NINDS epilepsy program is the public-private partnership known as the Anticonvulsant Screening Program (ASP). The ASP, established to identify and develop safer and more efficacious epilepsy therapies, has aided the development of many of the currently available treatment options. Since 1975, the ASP has tested over 25,000 compounds for anticonvulsant potential and established working partnerships with over 160 pharmaceutical companies and 250 academic institutions throughout the world. These efforts have most recently resulted in seven new ASP compounds being advanced through animal evaluations into human testing. The focus for the next five years is to develop novel agents for intractable forms of epilepsy and to find agents that prevent the development of epilepsy in those at risk for the disease.

Item

Parkinson's Disease (PD) - The Committee encourages NINDS, in addition to pursuing all promising therapeutic avenues, such as gene therapy, stem cells, surgical approaches, non-human models, and biomarkers, to continue to identify and study neuroprotectant compounds, such as Coenzyme Q10, creatine, and minocycline. Furthermore, the Committee encourages NINDS to work with NIBIB to discover a biomarker (particularly a molecular one) for Parkinson's. Participation by NIBIB in clinical trials could greatly enhance the value of these trials, as imaging technology facilitates a better understanding of the physical effects of tested drugs. Finally, the Committee commends NINDS for funding the Morris K. Udall Parkinson's Disease Research Centers of Excellence. These centers support additional research opportunities and discoveries that will lead to improved diagnosis and treatment of patients with Parkinson's disease. The centers vary in their basic and clinical objectives, but together they foster an environment that enhances research effectiveness in a multidisciplinary setting, (p. 79)

Action taken or to be taken

The NINDS is fully committed to exploring every scientifically promising lead to developing therapies for PD. For example, the NINDS-funded Parkinson's Disease Gene Therapy Study Group is making excellent progress, and has recently published research on a viral delivery system that can be regulated - a critical step in moving gene therapy to the clinic; the joint NINDS and Department of Veterans Affairs trial of deep brain stimulation for PD is still proceeding well, and investigators are planning to continue recruitment until April 2005. In addition, the NINDS-supported researchers running the Neuroprotection Exploratory Trials in

PD trial completed recruitment for their pilot studies of four potential neuroprotective compounds (Coenzyme Q10, creatine, minocycline, and a proprietary growth factor compound) ahead of schedule, and results are expected in 2005.

The NINDS recognizes that a biomarker for the presence or progression of PD would be an extremely valuable tool for clinicians and researchers. As a first step to explore the use of imaging tools as biomarkers in PD, the NINDS sponsored a workshop in July 2003 to consider the use of imaging as an additional measure or endpoint in clinical trials; the capabilities of current imaging technology, including molecular "tags"; and the feasibility of using imaging measures consistently in multicenter clinical trials. Participants and the NINDS staff have submitted a paper for publication that which outlines recommendations on: 1) methodological changes in studies to determine how imaging measures relate to clinical endpoints, and 2) development of new markers to better capture the degenerative process and more of the clinical features of PD. In a neurodegenerative disease, the ability to accurately measure small changes in disease progression can be important in assessing the effectiveness of therapies. Molecular imaging and other technologies that are accurate, sensitive, and specific are being developed. NINDS looks forward to working with the National Institute of Biomedical Imaging and Bioengineering (NIBIB) to validate new technologies should they appear promising.

Item

Transmissible spongiform encephalopathies (TSE) - The Committee recognizes the efforts of NINDS, in collaboration with NHLBI, to fund contracts for the development of a biological assay for TSE. The Committee requests that the Director of the Institute be prepared to provide a report on the progress made toward the development of a TSE bioassay at the fiscal year 2006 appropriations hearing. The Committee is particularly interested in the success in detecting disease-causing agents in blood, saliva, cerebrospiaal fluid, and other bodily fluids, as well as lymphoid tissue, especially tonsils, (p. 79)

Action taken or to be taken

The development of better tests to detect TSEs is critical for prevention programs and for therapeutic strategies. Current technology can reliably diagnose TSEs in tissues from animals and humans after death. Detection of TSEs in blood or other tissues from pre-symptomatic people or animals is stiil problematic, however, due to the unusual nature of the prion agent that causes TSEs. NIH supported researchers have developed highly sensitive tests for TSEs that can detect as little as one infectious unit per milliliter of blood. This will improve diagnosis of TSEs in brain tissue, but additional improvements in sensitivity are still required before these tests can be used to protect the blood supply. Although the goal of developing an improved test for TSEs remains a challenge, it is encouraging that the importance of addressing this issue has attracted the concerted effort of not only NIH, USDA, and Department of Defense supported scientists, but also of teams of researchers in Europe, as well as in dozens of private companies around the world.

Item

Peripheral neuropathy - The Committee is aware that an estimated 20 million Americans suffer from peripheral neuropathy, a neurological disorder that causes debilitating pain, weakness in the arms and legs, and difficulty walking. For most of its victims, the only recourse is pain medication, physical therapy or assistive devices to help maintain strength and improve mobility. In light of the large number of individuals affected and the attendant costs of this disease to society, the Committee encourages NINDS to develop a neuropathy research agenda, coordinated with work being done through other institutes, and report how much funding NIH is devoting to research in this area. The Committee expects to receive a report on this effort at next years hearings, (p. 79)

Action taken or to be taken

Peripheral neuropathy is a common neurological condition that is associated with a number of diseases. The National Institute of Neurological Disorders and Stroke (NINDS) funds a wide range of research on the peripheral neuropathies including diabetic neuropathy, HIV/A1DS-relatcd neuropathy, and Charcot-Marie Tooth disorder.

Over the past few years, NINDS, in collaboration with other institutes, has issued a number of initiatives, or Requests for Applications (RPAs) that have stimulated research in diabetic neuropathy. In addition, NINDS supports investigator-initialed projects including a large-scale, cross-sectional clinical and epidemiological study of neuropathic complications in diabetic patient populations and a pilot clinical study to lay the groundwork for a possible larger clinical trial to determine if glucose-lowering drugs or other interventions can prevent or stabilize the progression of diabetic neuropathy. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) also funds research relevant to diabetic neuropathy. The NIDDK's landmark clinical trial, the Diabetes Control and Complications Trial (DCCT), showed that maintaining blood glucose levels as close to normal as possible significantly slows the onset and progression of neuropathy and other complications of diabetes. The follow-on study to the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC), has further demonstrated long-term benefits of blood glucose control in substantially reducing the risk of diabetic neuropathy. The NIDDK also supports a Diabetes Research and Training Center at the University of Michigan, which developed several screening instruments for diabetes patients and health professionals, including one to screen for the presence of diabetic neuropathy.

In the area of HI V/AIDS-related neuropathy, NINDS funds research to uncover the mechanisms by which viral infection and/or anti-retroviral therapy contributes to neuropathy and the resulting neurotoxicity in certain cell types. The NINDS also supports research on various forms of Charcot-Marie Tooth disease, which is one of the most common hereditary and sensory neuropathies. Basic research aimed at understanding the underlying cellular and molecular mechanisms that are responsible for neuropathy is also supported by NINDS. Air understanding of these basic mechanisms may aid in the development of effective therapeutic strategies for these disorders. More broadly, a number of institutes at NIH, including NINDS, support a wide portfolio of research on pain; understanding the basic mechanisms of pain pathways and

modulation of pain may also be relevant to understanding and treating conditions like peripheral neuropathy.

The NIH funding for neuropathy research, which includes peripheral neuropathy, was $51.1 million in FY 2004. In FY 2005 and FY 2006, the estimated funding for neuropathy is S53.5 million and *$54* million respectively. The amount of money NLH spends on any one disease depends on scientific opportunity and the number of meritorious applications received in this area.

The NINDS is beginning to plan a workshop on the peripheral neuropathies. Researchers working in this area, as well as other institutes at NIH with an interest in the peripheral neuropathies, will be invited to participate. The goals of such a workshop will be to discuss and identify research goals aimed at improving our understanding of the peripheral neuropathies and identifying potential therapies for these disorders. This will be a first step towards the development of a research agenda for peripheral neuropathy.

Item

Dystonia- The Committee continues to support the expansion of research and treatment developments regarding the neurological movement disorder dystonia, the third most common movement disorder after tremor and Parkinson's disease. The Committee encourages NINDS to support research on both focal and generalized dystonia, and commends NINDS for its study of the DYT1 gene. The Committee commends NINDS for the release with other Institutes of the joint dysionia research program announcement. The Committee would like NINDS to be prepared to report on the dystonia research portfolio at the FY06 budget hearings. 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- (p. 79)

Action taken or to be taken

The NINDS continues to work with the dystonia research and voluntary disease communities to ensure that the needs of the research field are being addressed. The recent Program Announcement on dystonia has led to a number of new projects, on topics such as the developjncnt of animal models of primary and secondary dystonia, molecular and cellular studies of DYT1 dystonia, and brain imaging. In addition, NfNDS awarded funding in September 2004 to the Dystonia Medical Research Foundation, to provide partial support for a multi-year series of workshops focused on evolving areas of research that are critical for the development of therapeutics. These workshops will involve both experienced researchers and new investigators, and are expected to increase interest among investigators in the disorder, and expand collaborations in the field. NINDS has also participated in an October 2004 workshop to develop a strategic plan for a series of studies on the epidemiology of dystonia, and expects continued interactions with experts in the field as they develop their ideas and applications for funding.

llem

Spina bifida - The Committee encourages NJNDS to enhance research to address issues related to the outcome of the spina bifida conference held in May 2003 and to expand its research efforts in the prevention, and treatment of spina bifida and associated secondary conditions. The Director should be prepared to testify on NINDS efforts to advance these areas of research at the fiscal year 2006 appropriations hearing, (p. 80)

Action taken or to be taken

The NINDS funds a wide range of research projects relevant to spina bifida, many of which address recommendations of the May 2003 conference, Evidence-Based Practice in Spina Bifida: Developing a Research Agenda, held in Washington, DC. For example, NINDS-supported researchers are studying the causes and the cognitive effects of hydrocephalus, a build up of fluid in the brain that is common in spina bifida patients. The assessment and treatment of hydrocephalus emerged as a priority from the conference. NINDS also funds research aimed at understanding the neural bases of a variety of cognitive processes. This research is relevant to the neuropsychology and learning priorities set forth in the conference.

Basic research on the formation of the nervous system may help scientists to decipher the mechanisms underlying the development of spina bifida, and to devise strategies for preventing or treating the disorder. The NINDS funds grants to understand the genetic and environmental causes of spina bifida and to develop prevention and treatment strategics for the disease. Researchers are testing the hypothesis that certain genetic factors may diminish the availability of folale 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. NINDS supports a broad portfolio of research on understanding and treating spinal cord damage, whether due to spina bifida or other causes. Projects funded by NINDS include the development of pharmacological, electrical stimulation, and exercise interventions to improve locomotor and arm function, as well as the use of bioengineering strategies to restore function.

The NINDS helped support The Third International Conference on Neural Tube Defects (NTDs), held in September 2003, which brought together researchers from various disciplines to discuss recent advances in basic and clinical research on neural Lube defects, which include spina bifida. The principal investigator and organizer of the NTD conference, together with program staff, have organized banking of blood/DNA samples in an NIH repository, allowing sharing of these rare and important biological patient samples. In fall 2005, NINDS, along with ORD, NICHD and NIA, will sponsor a workshop entitled "Hydrocephalus: Myths, New Facts, Clear Directions" to build on collaborations developed at the NTD conference. This workshop will bring together researchers studying mechanisms of hydrocephalus, risk factors and related disorders and will identify research priorities for hydrocephalus.

Item

Spinal Muscular Atrophy (SMA) — SMA is the leading genetic killer of infants and toddlers. The Committee understands that the severity of the disease, its relatively high incidence, and the possibility of imminent treatments have led NINDS to initiate the SMA Therapeutics Development Program. The Committee is pleased that initial work has begun on (he program and encourages NINDS to move forward with the mission to develop a treatment for SMA to be ready for clinical trials within four years. The Committee further encourages NINDS to develop a strategy for executing effective clinical trials for future therapies. The Committee encourages NINDS to integrate therapeutics development efforts with the biotech and pharmaceutical industry, academic medical centers and collaborations with voluntary health organizations, (p. 80)

Action taken or to be taken

The NINDS remains committed to supporting the SMA Therapeutics Development Program, and the program is on track to develop a treatment for SMA that can enter clinical trials within four years. The NINDS awarded the primary contract to provide overall scientific and organizational support in September 2003. The Steering Committee, with expert members from academia, industry, the FDA, and the NIH, developed a research plan and priorities for the research projects to be conducted under the contract. As of October 2004, subcontracts have been awarded to develop an inducible mouse model of SMA that can be used to identify the therapeutic window; motor neuron cell culture models of SMA, to be used for identifying and testing potential drugs; and a standardized method for measuring SMN levels that can be widely used in laboratory and clinical research (SMA patients have reduced levels of the SMN gene product). In June 2004, the program released Requests for Proposals to establish facilities for testing potential drugs in cellular and mouse models and for medicinal chemistry studies.

The NINDS continues to support the development of outcome measures and biological markers that will expedite clinical trials. An Institute supported network of investigators is also conducting pilot trials of drugs that are now available and have potential for treating SMA. In September 2004, the NINDS held a workshop on clinical trials for SMA. Representatives from the biotech and pharmaceutical industry, academia, and voluntary patient organizations joined government officials in discussing the requirements for and obstacles to initiating clinical trials in SMA. Working groups developed action plans to prioritize candidate drug therapies for use in clinical trials, identify primary outcome measures and other issues in clinical trial design, and develop collaborative research paradigms.

Item

Down syndrome- Recently Down syndrome research has begun to focus increasingly on understanding the effect the disorder has on gene expression, cell function, neurons and neural systems. The Committee strongly encourages NTNDS to expand its research on Down syndrome, particularly as it relates to gene expression in the brain and the development of possible biomedical interventions to improve cognition, memory, speech, behavior, and to

prevent early dementia. The Committee further encourages NINDS to assume a leadership role in coordinating this research among the Institutes and to work closely with NICHD to address the serious shortage of mice used for Down syndrome research, (p. 81)

Action taken or to be taken

The NINDS is actively engaged in supporting research to address Down syndrome, the most frequent cause of miid to moderate mental retardation. The Institute funds research which utilizes state of the art imaging and recording techniques to study the neLiroanatomical and physiological abnormalities in Down syndrome brain development. Other research funded by NINDS is investigating the genetic and molecular basis for the degeneration of specific neuronal populations in the brains of adult Down syndrome patients. Several research projects focus on the role of specific genes and proteins in Down syndrome, including one profiling the types and levels of proteins that are present in Down syndrome versus normal brain tissue.

In addition to the research it supports, the NINDS is working with other Institutes to bring researchers together to facilitate scientific discovery. The NINDS, together with NICHD, NIA and NIMH, is sponsoring a workshop entitled "Down Syndrome: Towards Optimal Synaptic Function and Cognition" in early 2005. Given recent scientific advances in the understanding of Down syndrome, the goal of the workshop is to promote the development of treatments for the cognitive abnormalities that accompany the disease, thereby improving functional outcomes for Down Syndrome patients,

The NINDS recognizes the importance of ensuring the availability of Down syndrome mouse models and supports efforts by NICHD to increase production of this strain. In addition, the NINDS has nominated the Down syndrome mouse model for distribution through the Mutant Mouse Regiona] Resource Centers repository, an NIH-sponsored repository which preserves and distributes valuable genetic mouse strains for use by the scientific community.

Item

Mucoiipidosis Type IV (ML4) —Since the gene causing this debilitating genetic metabolic disorder has been identified, the Committee encourages the NINDS to support both extramural and intramural research which will lead to possible treatments and cures for those with ML4. In particular, NINDS is encouraged to conduct research involving other organisms which bear genes resembling the one whose mutation in humans causes ML4. (p. 81)

Action taken or to be taken

Researchers supported by the NINDS were among those who discovered that defects in the MCOLN1 genes are responsible for ML4, and NINDS continues to support research on how the mutations contribute to ML4 pathophysiology. An ongoing extramural project is detennining the cellular function of the MCOLN1 gene family using animal and cellular models and gene expression analysis. The NINDS intramural research program is conducting a natural history study of ML4, which may lead to a better understanding of the disease and the medical difficulties of patients and to better ways of diagnosing ML4.

The NINDS has also taken special actions to promote research on lysosomal storage disorders, including ML4. In FY04, the NINDS, the NIH Office of Rare Diseases, and the Lysosomal Storage Disease Research Consortium released a Program Announcement with set-aside funding to support the development of central nervous system-targeted therapies for lysosomal storage disorders. The NINDS also sponsored several 2004 workshops on lysosomal storage disorders, with the goal of stimulating research in this field. The *Annual Symposium WORLD Lysosomal Diseases Clinical Research Network* in May provided an interdisciplinary forum to explore and discuss specific areas of interest related to Jysosomal diseases, including longitudinal study design, quality of life assessment, bioethics, regulatory issues, and innovative therapies. A May workshop entitled *Lysosomal Diseases and the Brain* updated the research community on recent advances of the pathogenesis and therapy of these disorders. An October workshop on *Brain Uptake and Utilization of Fatty Acids, Lipids and Lipoproteins: Applications to Neurological Disorders* assessed the state-of-the-science in brain fatty acid/lipid uptake and utilization and discussed progress in understanding molecular mechanisms and the treatment of neurological diseases such as ML4.

Item

Mucopolysaccaridosis (MPS) —The Committee encourages the NINDS to collaborate with all appropriate Institutes and Centers to support mucopolysaccharidosis research, to study the blood-brain barrier as an impediment to research, and to use all available mechanisms to further stimulate and enhance efforts to better understand and treat MPS disorders, (p. 81)

Action taken or to be taken

The NINDS has taken several actions to address blood-brain barrier issues in order to help accelerate therapy development for diseases like MPS. In FY 2004, NINDS, in collaboration with the NIH Office of Rare Diseases (ORD) and the Lysosomal Storage Disease Research Consortium, released a Program Announcement with set-aside funding to support the development of central nervous system-targeted therapies for lysosomal storage disorders. This announcement specifically encourages research for improved delivery of therapeutic cells, proteins, genes, and small molecules across the blood-brain barrier. In FY 2003, NINDS released a program announcement with set-aside funding to solicit research on the biology of the blood-brain barrier and strategies to deliver therapeutic agents across it; NINDS continues to receive applications under this program announcement. These initiatives responded to recommendations from the NTNDS-sponsored workshop on MPS in 2002.

The NINDS is currently funding several laboratories to develop therapeutics strategies for MPS. Ongoing grants support the development of gene therapy strategies for MPS type VII (Sly disease). A new project initiated in FY 2004 is aimed at developing a novel enzyme replacement strategy for MPS 111 (San Filippo syndrome) that will enable the therapeutic enzyme to cross the blood-brain barrier. Another new project is exploring the potential use of stem cells from bone marrow to treat MPS I (Hurler syndrome). In addition, NINDS funds basic and cross-cutting research that will be crucial for progress in MPS, as well as for many other diseases, including

active programs in neural stem cell research, pediatric ncuroimaging, and translational research, which brings basic research discoveries to bear on therapy development.

The NINDS sponsored several 2004 workshops on lysosomal storage disorders, with the goal of stimulating research in this field. The NINDS, together with the NIH ORD and the International Society for Mannosidoses and Related Disorders, sponsored an April 2004 workshop on glycoproieinoses, which included several talks on MPS. The *Animal Symposium WORLD Lysosomal Diseases Clinical Research Network* in May provided an interdisciplinary forum to explore and discuss specific areas of interest related to lysosomal diseases, including longitudinal study design, quality of life assessment, bioethics, regulatory issues, and innovative therapies. Another May workshop entitled *Lysosomal Diseases and the Brain* tipdated the research community on recent advances of the pathogenesis and therapy of these disorders. An October workshop on *Brain Uptake and Utilization of Fatty Acids, Lipids and Lipoproteins: Applications to Neurological Disorders* assessed the state-of-fhe-science in brain fatty acid/1 ipid uptake and utilization and discussed progress in understanding molecular mechanisms and the treatment of neurological diseases such as MPS,

FY 2006 Senate Appropriations Committee Report Language CS. Rpt. 108-345)

Item

Alzheimer's disease - The NINDS continues to play an integral role in widening the scientific base of knowledge about Alzheimer's disease. One emerging theme in the study of Alzheimer's disease and other neurodegenerativc diseases such as Parkinson's and Huntington's disease, is the overlap researchers have observed in the pathology underlying these conditions. Scientific reports are showing evidence that these disorders may be caused by similar abnormalities in protein folding and accumulation, making support for Alzheimer's disease research more relevant than ever. On another front, working with NIA in the area of immunotherapy for Alzheimer's disease, the NINDS has funded a collaborative group of Alzheimer's disease centers that will investigate the differences which can involve the production of antibodies that reduce the cellular and behavioral effects of the disease. The Committee encourages N1NDS to continue to assign a high priority to its Alzheimer's research portfolio, and to work closely with NIA and other institutes. The Committee also encourages NINDS to conduct large scale clinical trials that will identify therapies and treatments capable of slowing or halting the onset and progression of Alzheimer's, (p. 117)

Action taken or to be taken

The NINDS has continued to explore many aspects of Alzheimer's disease research, including but not limited to abnormalities in protein folding that may also occur in other ncurodegenerative conditions and immunotherapy for AD. Emerging areas of research include naturally-occurring enzymes that may modulate the cellular levels of amyloid protein found in the brains of AD patients; the link between cholesterol and AD; and prcclinical development of therapeutic agents, such as drug therapies that target the tail protein component of neurofibrillary tangles, another hallmark of nerve cells affected by AD.

A critical goal of the NINDS investment in AD research is the development of new treatment options for individuals with AD. However, the infrastructure within the National Institute on Aging (NIA) Alzheimer's Disease Center program is best-equipped to conduct large-scale clinical trials of potential treatments; and at present, most investigators in the field utilize this resource. To complement the NIA investment in clinical research, NINDS is currently supporting both pre-clinical and translational research on topics such as those listed above, that hopefully will expand the pool of therapeutic agents to be tested. For example, one NINDS-funded researcher has very recently published a study exploiting one of the Jess-investigated routes for decreasing amyloid buildup in the brain. Specifically, she has tested a drug that interferes at a specific point in the cholesterol pathway that makes a strong contribution to the generation of amyloid, and has demonstrated a 99% reduction in brain amyloid in a mouse model of the disease. If these results can be replicated, this finding suggests a novel approach for developing a therapeutic intervention for AD. As the NINDS translational and clinical research programs expand, and as the field of AD moves forward, NINDS will look for opportunities to become more involved in the support of meritorious clinical trials, through promising collaborations with NIA, or through direct funding, if appropriate under the scientific mission of NINDS.

As in the past, NINDS continues to collaborate with NIA and other NIH Institutes and Centers with an interest in AD. In September 2004, the NINDS and NIA jointly sponsored a workshop on the clinical and pathological overlap of "Parkinson's disease plus dementia" and "dementia with Lcwy bodies." As the name suggests, Parkinson's disease plus dementia often presents in individuals with presumptive PD, dementia with Lewy bodies has parkinsonian features, and there is a Lewy body variant of Alzheimer's disease. There is probably a close biological relationship among these disorders. Investigators and clinicians supported by NINDS and NIA are eager to do more to understand this relationship, and a number of promising avenues of collaboration emerged from this workshop. In addition to this event, NINDS also joined the NIA on its re-release of a Request for Applications (RFA) entitled "Collaborative Studies on Alzheimer and Related Diseases" in September 2004. Following the initial release of this RFA in 2002, NINDS funded a highly meritorious award to a group of Alzheimer's Disease Centers that investigated the differences between AD and dementia with Lewy bodies.

Item

Alzheimer's Disease and Early Diagnosis- 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. 117)

Action taken or to be laken

The NINDS continues to support imaging studies that might provide earlier diagnosis of AD, and potentially permit earlier intervention. Currently-funded studies are exploring the use of positron emission tomography (PET) and functional magnetic resonance imaging (MRI) to examine plaques and tangles, the cellular hallmarks of AD, in individuals with a genetic predisposition to the disorder; the use of MRI to determine if the degeneration of specific brain regions may be a

hallmark of pre-clinical AD; and the use of MRI to evaluate changes in brain function that are exhibited by individuals with mild AD as they complete specific memory tasks.

In addition to these research studies, the NINDS also funded a project in September 2003 designed to examine the complex ethical issues surrounding advanced imaging of the nervous system. Specifically, one part of this project will explore the ethical challenges in predicting subclinical AD using techniques like MRI; these challenges include the medical and social consequences of imaging; informed consent; privacy issues; and counseling, to name just a few.

With regard to collaboration, NINDS joined the National Institute of Mental Health, the National Institute on Aging (NIA), and several other N1H Institutes on a Program Announcement, released in April 2003, which 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.

In addition to these activities, the NIA has been consulting closely and regularly with the Centers for Medicare and Medicaid Services (CMS) on the issue of neuroimaging in the diagnosis of AD, including the related CMS coverage decision in September 2004. In addition, the NIA, in conjunction with other Federal agencies and private companies and organizations, recently launched a $60 million, five year public-private partnership - the Alzheimer's Disease Neuroimaging Initiative (ADNI) - to collect data on serial MRI, PET, other biological markers, and clinical and neuropsychological assessments. Scientists will be able to access this public database to explore the best measures for the early diagnosis and progression of mild cognitive impairment and AD. The ADNI has been a subject of specific discussion between NIA and CMS, as the ADNI might be considered for use as an initial step towards collecting the kind of data CMS would find useful. The NINDS will provide timely notice to the CMS and the NIA on any results it supports in this area, so that CMS can continue to be fully informed on the issue.

Ilem

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. 117)

Action taken or to be taken

The N1H helped support the discovery of the Ataxia Telangiectasia Mutated (ATM) gene defect that causes A-T, and several NIH Institutes, including the NINDS, continue to fund research aimed at understanding the normal functions of the ATM gene and how defects cause disease. NINDS funds research on the role of ATM specifically in the nervous system; the National Cancer Institute (NCI) supports studies on the relationship between mutant versions of ATM and the development of cancer; the National Institute of General Medical Science (NIGMS) funds

several studies on the mechanism of action of A T M in normal cells, and research supported by the National Heart, Lung, and Blood institute (NHLBI) addresses the role of A T M in the normal and abnormal growth of cardiac tissue.

In addition to supporting basic research on A-T, the NINDS funds research more directly aimed at therapeutics development. One team of NINDS-funded researchers are developing a genetically engineered rhesus monkey model of A-T that can be used to test gene and stem cell-based therapies; another is exploring the possibility of using combinations of drugs to promote the production of functional A T M protein in celi culture models of A-T. The NINDS awarded a new grant in FY 2004 to develop and test a gene therapy strategy in a mouse model of A-T. The NINDS also suppoits a facility that conducts high-throughput drug screens for neurodegenerative disorders, including A-T. In October 2004, the NINDS, NTH OORD, and A-T Children's Project co-hosted a workshop to consider innovative approaches to high-throughput A-T drug screening that could be adopted by the NINDS facility. The NINDS is also working with NCI and the National Human Genome Research Institute (NHGRI) to identify successful aspects of NCI cancer dmg screening programs and the NIH Roadmap molecular library screening program that could be applicable to 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 expects to be informed of the steps taken to increase research on Batlen disease, (p, 117)

Action taken or to be taken

The NINDS supports a diverse research portfolio on Batten disease, which generally refers to a group of disorders know as Neuronal Ceroid Lipofuscinoses (NCLs). The portfolio includes studies of the molecular pathways underlying the disease, the effects of the disease at the cellular and subcellular levels, the development of animal models, and preclinical testing of potential treatments, with new grants on gene and stem cell therapies. The NINDS has also taken special actions to promote research on lysosomal storage disorders, including Batten. In FY04, the NINDS, NIH Office of Rare Diseases, and Lysosomal Storage Disease Research Consortium released a Program Announcement with set-aside funding to support the development of central nervous system-targeted therapies for lysosomal storage disorders. 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 treating this disease.

The NINDS sponsored several workshops in 2003 and 2004 on lysosomal storage disorders, which include Batten, with the goal of stimulating research in this field. In November 2003, NINDS sponsored a workshop that explored the implication of data suggesting that juvenile Batten may be an autoimmune disorder. The *Annual Symposium WORLD Lysosomal Diseases Clinical Research Network* in May 2004 provided an interdisciplinary forum to explore and

discuss specific areas of interest related to lysosomal diseases, including longitudinal study design, quality of life assessment, bioethics, regulatory issues, and innovative therapies. Another May 2004 workshop entitled *Lysosomal Diseases and the Brain* updated the research community on recent advances of the pathogenesis and therapy of these disorders. An October 2004 workshop on *Brain Uptake and Utilization of Fatty Acids, Lipids and Lipoproteins: Applications to Neurological Disorders* assessed the state-of-tlie-science in brain fatty acid/lipid uptake and utilization and discussed progress in understanding molecular mechanisms and the treatment of neurological diseases related to lipids and lipoproteins.

In 2004, NINDS also awarded the prestigious Javits Neuroscience Investigator Award to an investigator who studies infantile NCL, The seven year duration of the award will provide the investigator with three more years of funding than a typical R01 grant, allowing the investigator to develop a longer term research project on NCL.

Item

Brain tumors —The Committee continues to be concerned that not enough attention and resources are devoted to identifying causes of and treatments for brain tumors and encourages NFNDS to continue working with NCI to carry out the recommendations of the Report of the Brain Tumor Progress Review Group, (p. 118)

Action taken or to be taken

Brain tumor research continues to be a priority of the NINDS, and the Institute is supporting a variety of activities, many in collaboration with the National Cancer Institute (NCI), that address recommendations in the Report of the Brain Tumor Progress Review Group (BT-PRG). The NINDS and NCI have issued several relevant grant solicitations. In March 2004, the NINDS and NCI released *a* Program Announcement with set-aside funding (PAS) to promote the understanding and prevention of brain tumor cell migration; this PAS responded to a specific BT-PRG recommendation. The NINDS issued a PAS in FY 2003 to stimulate research on the blood-brain barrier—deemed an especially high priority by the BT-PRG—and continues to accept grant applications under this solicitation. A 2002 Program Announcement led NINDS and NCI to jointly support a Specialized Program of Research Excellence (SPORE) on brain tumors. This SPORE focuses on therapeutics development, strategics to overcome chemotherapy resistance, and identification of environmental risk factors for gliomas, which constitute approximately half of all primary brain tumors and are particularly lethal.

The NINDS and NCI also jointly supported the Brain Tumor Genome Anatomy Project (BTGAP), which addressed BT-PRG recommendations to support genomic studies. BTGAP developed comprehensive molecular profiles from a collection of primary brain tumors at progressive levels of malignancy. To expand this effort, the two Institutes are now developing a large-scale, multifunctional database (called REMBRANDT) that will store molecular and linked clinical information from brain tumor samples. This database will allow investigators throughout the world to share and manipulate this data. A pilot version of REMBRANDT will be released in November, 2004.

Many ongoing, investigator-initiated projects also address recommendations of the BT-PRG. NINDS-funded investigators arc 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; clinicai trials to test the safety and efficacy of the new approaches; and the development of new neuro imaging tools and animal models for brain tumor research and diagnosis.

In addition to supporting research, NINDS also supports regular workshops to help accelerate the field of brain tumor research. The NINDS sponsored a workshop in September, 2004, to promote the use of evidence-based interventions in the evaluation, treatment, and assistance of patients with brain disorders affecting higher thought processes. Brain tumor was one of three disorders covered in this workshop, with a focus on rehabilitation of memory and attention mechanisms.

Item

Down syndrome - Recently Down syndrome research has begun to focus more on understanding the effect the disorder has on gene expression, cell function, neurons and neural systems. The Committee strongly encourages NINDS to expand its research on Down syndrome, particularly as it relates to gene expression in the brain and the development of possible biomcdical interventions to improve cognition, memory, speech, behavior, and to prevent early dementia. The Committee further encourages NINDS to assume a leadership role in coordinating this research among the Institutes and to work closely with NICHD to address the serious shortage of mice used for Down syndrome research, (p. 118)

Action taken or to be taken

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

Item

Epilepsy - The Committee strongly encourages the Institute to expand its efforts to find breakthroughs in the prevention, treatment, and eventual cure of epilepsy. The Committee applauds the development of benchmarks for epilepsy research resulting from the "Curing Epilepsy: Focus on the Future' conference held in March 2000. The Committee expects that NINDS will continue to update Congress and the public on progress in reaching these goals. The Committee further encourages the Institute to address critical research issues raised at the Living Well With Epilepsy II conference held in July 2003, These investments in our Nation's health examine how epilepsy begins, ways of identifying people at risk and how to develop treatments that will prevent epilepsy in those people, as well as continuing the search for new therapies, free of side effects, to prevent seizures. In addition, the Committee urges the NINDS to focus on the critical research issues relating to the over 30 percent of patients with intractable epilepsy, to the life-long impact of seizures on young children, and to the growing incidence of epilepsy in the elderly. The Committee encourages the Institute to continue its anti-epileptic drug development program to discover therapies that may provide answers for the large number of people who do

not respond to current treatments. The Institute is expected to update the Committee on its plans to advance these critical areas of research at the fiscal year 2006 appropriations hearing, (p. 120)

Action taken or to be taken

Please refer to page NINDS-33 of this document for the NINDS response to this significant item regarding epilepsy research.

Item

Fragile X - Fragile X is a single-gene disorder, but both its symptoms and its cellular mechanisms suggest involvement of multiple genes and specific brain pathways which are associated with other neurological disorders, such as autism and seizures. Furthermore, recent research offers clear evidence for disruption of fundamental brain circuitry in Fragile X. Research on Fragile X has the potential to contribute to understanding of multiple disorders. The Committee urges NINDS to expand its research activities on Fragile X and to coordinate these efforts with other Institutes working on related activities, including NIMH and NICHD. (p. 120)

Action taken or to be taken

The NINDS funds several grants to characterize the genetic and biochemical causes of Fragile X syndrome, the most common cause of inherited mental retardation. The disease is associated with a mutation in a single gene cased FMR1 which resides on the X chromosome. One study uses a unique and powerful fruit fly model system to identify and characterize additional genes involved in the disease. The long term goal of the project is the development of improved therapeutic interventions for Fragile X syndrome. In addition, research funded by the NINDS on the causes and treatments of mental retardation may benefit individuals with Fragile X syndrome.

The NIH fosters communication among Fragile X researchers from different institutes through meetings, workshops and shared research projects. NINDS, together with the National Institute of Mental Health (NIMH) and the National Institute of Child Health and Human Development (NICHD), sponsored a workshop in July 2004 entitled "At the Crossroads: Common Pathways in Fragile X and Autism" on the overlap between these and other neurodevelopmental disorders. Collaborative research between NINDS- and NICHD-funded investigators has led to major recent discoveries about the causes of Fragile X syndrome, including one study that identified a novel activity for the FMR1 protein which is disrupted by the Fragile X mutation. In addition, NINDS and NICHD fund research on Fragile X-associated tremor/ataxia syndrome (FXTAS), a newly identified disorder which affects older male carriers of a mutation in the gene which causes Fragile X syndrome.

Item

FXTAS - Fragile X-associated tremor/ataxia syndrome, or FXTAS, is a newly discovered, progressive neurological disorder that affects older men who are earners of a premutation in the same gene that causes Fragile X syndrome, the most common cause of inherited mental retardation. Nearly 1 in 800 men in the general population carries this premutation in the Fragile

X gene, and as many as 30 percent of those **carriers**—roughly 1 in 3,000 men—may develop FXTAS later in life. NINDS, in collaboration with the National Institute on Aging, is urged to commit additional resources and expand research into FXTAS, as identification of older male carriers will lead to a better understanding of the true incidence of Fragile X syndrome and afford at-risk families of child-bearing age the opportunity to pursue genetic counseling, (p. 120)

Action taken or to be taken

The NINDS funds several grants to further define and understand Fragile X-associated tremor/ataxia syndrome (FXTAS). One study is following a group of affected and unaffected men, with and without the mutation, in order to define clinical features and disease progression of FXTAS. Another investigator, jointly funded by NINDS and the National Institute of Child Health and Human Development (NICHD), is examining individuals over 50 years of age of both genders for the presence of the mutation and for FXTAS symptoms. Interestingly, this project has identified several rare cases of FXTAS in women. Since the researchers estimate that up to thirty percent of carriers may develop the disorder later in life, the goal of the research is to understand who among mutation carriers is likely to develop FXTAS so that they may undergo treatment for and genetic counseling about FXTAS and the likelihood of future generations developing Fragile X syndrome.

In addition, the NINDS, NICFID, the National Institute on Aging (NIA), and the National Institute of Mental Health (NIMH) fund research on movement disorders, including the ataxias, and on Fragile X syndrome, which may be relevant to the study and treatment of FXTAS.

Item

Interdisciplinary Research - The Committee encourages NINDS to continue exploring novel pathways by which cognitive neuroscicntists 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 Committee applauds NINDS for promoting the establishment of milltidisciplinary teams of scientists including neurologists, cognitive functional imaging experts and computational modelers in order to accelerate progress in the field of cognitive rehabilitation. By focusing on the limited set of neurological conditions (stroke, traumatic brain injury, and brain tumor) where these partnerships are likely to produce realistic gains in higher level functioning, NINDS may provide a model for interdisciplinary approaches to a range of conditions in which residual capacity is more difficult to measure, (p. 121)

Action taken or to be taken

On September 23-24, 2004, the NINDS held a meeting entitled "Cognitive Rehabilitation Interventions: Moving from Bench to Bedside." The goal of this workshop was to promote the use of evidence-based interventions in the evaluation, treatment, and assistance of patients with disorders of the brain affecting higher thought processes. The workshop brought together multidisciplinary teams of scientists including neurologists, cognitive neuroscientists, psychologists, occupational therapists, pharmacologists, functional imaging experts and

computational modelers in order to accelerate progress in the field of cognitive rehabilitation. Three teams were formed prior to the workshop to address the following areas: (1) Brain Tumor: Cognitive Deterioration / Rehabilitation of Memory and Attention Mechanisms; (2) Stroke: Unilateral Neglect / Rehabilitation of Spatial Attentionai Disorder; and (3) Traumatic Brain Injury: Executive Function / Rehabilitation of Regulatory Cognitive Processes. Each team developed a white paper, which summarized the state of the science and made recommendations to address these three areas in the future. The N1NDS will be working to follow-up on the discussions and recommendations from this meeting, with the immediate goal of stimulating research into more effective interventions, and with the longer range goal of determining how to better translate cognitive neuroscience findings into the clinic.

The NINDS also supports research aimed at treating the cognitive effects of other neurological disorders. In May 2002, NINDS, along with three other NTH institutes, issued a PA-S (program announcement with set-aside funds) entitled, "Basic and Translational Research on the Cognitive Sequelae of Parkinson's Disease." A major goal of this PA-S is to begin a process where basic and clinical scientists from various disciplines can overcome barriers to cross-disciplinary research and examine all aspects of cognition in the context of the diagnosis and treatment of Parkinson's disease. The NINDS has funded four projects so far from this PAS. These include studies focused on the neural basis and regulation of behavior, decision-making, and executive functions such as complex reasoning and emotiona? control in patients with Parkinson's disease.

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 juvenile diabetes. The Committee encourages the NINDS to continue to expand its research into neuropathy and hypoglycemia unawarcness and lo consider establishing centers focused specifically on diabetic neuropathy. The Committee requests an update during the fiscal year 2006 hearings on the current status of diabetes-related research programs being earned out by the Institute and also urges the NINDS to organize a workshop focusing on diabetic neuropathy. Such a workshop would provide the research community with an opportunity to identify common goals toward the development of novel clinical treatments for diabetic peripheral and autonomic neuropathies, (p. 121)

Action taken or to be taken

Peripheral sensory neuropathy is a common neurological condition which is associated with diabetes as well as other disorders. A number of initiatives, or Requests for Applications (RFAs), issued by NINDS, in collaboration with other institutes, over the past few years have stimulated research in diabetic neuropathy. These initiatives, issued in 1998, 2000, and 2001 focused on the effects of diabetes on functioning of the nervous system. More recently, in FY 2003, NTNDS co-sponsored, along with other NIH Institutes and Centers, four RFAs aimed at understanding and treating type 1 diabetes and its complications. These initiatives have resulted in a number of NINDS-fundcd projects in diabetic neuropathy including two recently-funded studies focused on understanding the mechanisms of neuronal death as a result of hypoglycemia

and ways to prevent this cell death from occurring, as well as studies aimed at identifying possible targets for therapeutic intervention.

Research centers are only one of the many ways that N1H can support research. Research centers require a large investment of resources, often at the expense of a more multi-faceted approach to understand and treat a disease. The initiatives mentioned above, as well as investigator-initiated research, have been successful means to encourage a wide range of research into diabetic neuropathy and its complications. Other projects funded by N1NDS in this area include a large-scale, cross-sectional clinical and epidemiological study of neuropathic complications in diabetic patient populations and a pilot clinical study to understand and characterize Impaired Glucose Tolerance (JGT)- associated neuropathy (IGT represents an intermediate defect in glucose metabolism). This trial will lay the groundwork for a potential larger clinical trial to determine if glucose-lowering drugs or other interventions can prevent or stabilize the progression of diabetic neuropathy.

The NINDS also funds a wide range of basic research on understanding and treating other peripheral neuropathies, including HIV/AIDS-related neuropathy and Charcot-Marie-Tooth disorder. Much of this research may be relevant to understanding and treating diabetic neuropathy as well. The NINDS is beginning to plan a conference on the peripheral neuropathies to bring together researchers working on all forms of peripheral neuropathy, including diabetic neuropathy. The goals of such a conference will be to discuss and identify research goals aimed at improving our understanding of the peripheral neuropathies and identifying potential therapies for these disorders.

Item

Multiple Sclerosis (MS) - The Committee recognizes that more than 350,000 people in the United States currently suffer from multiple sclerosis and that approximately 200 new cases are diagnosed each week. The cause of MS remains unknown and no cure exists. The Committee urges NINDS to coordinate with private organizations that are working to discover effective treatment targets for MS. (p. 121)

Action taken or to be taken

A recent set of collaborations between the NINDS, pharmaceutical companies, and the National Multiple Sclerosis Society (NMSS) are an excellent example of the benefit of leveraging resources between public and private research sponsors. The NINDS has awarded a grant to conduct a large scale Phase 1l1 multi-site clinical trial of "Combination Therapy in MS" (the CombiRx trial) to test the effectiveness of the single drugs interferon-beta and copaxone versus the combination of both drugs in treating relapsing forms of MS. The manufacturers of interferon-beta (Biogcn IDEC Phannaceuticals) and copaxone (Teva Phannaceuticals LTD) have partnered with NINDS to provide the drugs for the study. The NMSS will provide support for an ancillary study of visual acuity to be added to the main CombiRx trial. NINDS intramural investigators will conduct a large biomarker study (BioMS) that will make use of the clinical data collected in the Phase III trial. Together these cost-effective partnerships enhance the scientific information to be gained from the CombiRX trial.

The NINDS also maintain regular communication with private groups such as NMSS through its membership on the NIH the Autoimmune Diseases Coordinating Committee (ADCC). Led by the National Institute of Allergy and Infectious Diseases (NIAID), the ADCC facilitates collaboration among NIH Institutes, other Federal agencies, and private organizations with an interest in autoimmune diseases.

The NINDS and the NIAID have worked collaboratively with the NMSS on a number of activities, including a joint initiative in 2001 ("Sex Based Differences in the Immune Response") and a joint workshop in 2003 ("Genetics and Multiple Sclerosis: Future Prospects"). In April 2004, the NINDS held a workshop on "Biomarkers in MS" in which the NMSS also participated. Attendees included scientists from several NIH Institutes (including NIAID), representatives from the NMSS, and academic and industry experts from around the world. In October 2004, the NINDS released a Program Announcement (PAS-05-002: Axonal Damage in Multiple Sclerosis: Strategics for Protection and Repair) to request translational research proposals to follow up on the NMSS workshop on "Myelin Repair: Is It Possible?" held in March 2002.

Building on this productive history, the NINDS, the NIAID and their NIH partners continue to welcome the opportunity to collaborate with the NMSS, pharmaceutical sponsors and with other private organizations toward the shared goal of finding effective therapies and ultimately a cure for MS.

Item

Neurofibromatosis—Advances in NF research have linked NF to cancer, brain tumors, learning disabilities, and heart disease affecting over 150 million Americans. Because NF plays a pivotal role both in disorders of the brain and in cancer and the enonnous promise of NF research is now reaching fruition in the testing of potential therapies, the Committee encourages NINDS to aggressively expand its clinical and basic research portfolios. The Committee commends the NINDS for its leadership role in NF research and in coordinating efforts with other Institutes engaged in NF research. The Committee applauds NINDS and the Office of Rare Diseases for convening a major conference on NF in December 2003. The Committee also applauds NINDS on issuing major program announcements in fiscal year 2004, pursuing the creation of NF research centers and NF translational research. The Committee encourages NINDS to follow through with the creation of these centers, (p. 121)

Action taken or to be taken

The NINDS continues to support a varied portfolio of investigator-initiated research on neurofibromatosis (NF), including studies on the molecular pathways through which the NF1 and NF2 gene products control cell proliferation and migration, the mechanisms by which particular types of tumors form in NF patients, the correlation between mutations and symptoms in NF patients, and how NF mutations lead to learning disabilities. To encourage the translation of this basic research into therapies, NINDS issued a program announcement in November 2003 to solicit applications for NF research centers; each center must propose three projects, at least one of which must be translational or clinical in nature. Applications for the first receipt date

have been received and currently are undergoing peer review. Applications can also be submitted over the next few years under this solicitation.

The NiNDS has also supported several recent conferences on NF. The NINDS and the NIH Office of Rare Diseases (ORD) cosponsored *a* December 2003 workshop, "Accelerating Therapy Development for N euro fib romatosis," which identified roadblocks to drug development and suggested strategies for eliminating them. The NINDS continues to provide funding, after competitive review, for the annual meetings of the NNFF International Consortium for the Molecular Biology of NF1 and NF2. These annual meetings have been held for more than a decade and have spawned key collaborations in NF research. In addition, in conjunction with the Department of Defense and the ORD, NINDS sponsored a September 2004 workshop to develop a strategy for creating standing infrastructure for NF clinical trials.

Item

Neuroprosthetics - The Committee urges the Institute to expand research on neuroprosthetics, such as the Brain Machine Interface (or Human Assisted Neurological Device) project. This research offers great promise in restoring movement in individuals suffering from a variety *of* neurological disorders including paralysis, stroke and wound-related trauma, (p.121)

Action taken or to be taken

For three decades, the NINDS Neural Prosthesis Program has fostered pioneering work on devices that connect to the nervous system to compensate for abilities lost through disease or injury. The Institute continues to encourage progress in this area through grant and contract programs. This fall, the Neural Prosthesis Program held its 35th Annual Meeting, an event that has a strong record of stimulating progress and cooperation in this dynamic and expanding Held. The meeting was supported through the cooperative efforts of the NINDS, the National Institute for Biomedical Imaging and Bioengineering, the National Institute of Child Health and Human Development, the National Institute on Aging and the National Institute on Deafness and Other Communication Disorders.

The NINDS supports research on a wide range of neurological devices, including functional stimulation devices and implanted cortical microelectrodes. Recent progress in the development of implanted cortical devices has been truly exciting. Research efforts conducted by NINDS grant and contract recipients have demonstrated that a system that combines implanted electrodes and compute)- programs can enable monkeys to instantaneously control a cursor on a computer screen and a robotic limb by thought alone. A system has now been approved for investigational use in a small clinical feasibility study in human quadriplegic patients.

Item

Peripheral Neuropathy -The Committee is aware that an estimated 20 million Americans suffer from peripheral neuropathy, a neurological disorder that causes debilitating pain, weakness in the arms and legs, and difficulty walking. Peripheral neuropathy affects approximately one-third of diabetics, or about 5.1 million persons. Other forms of neuropathy are inherited; associated with

cancer, kidney disease or infections like hepatitis, HIV/AIDS or Lyme disease; or caused by autoimmunity, traumatic injuries, poor nutrition, toxins and certain medications. For most of its victims, the only recourse is pain medication, physical therapy or assistive devices to help maintain strength and improve mobility. *In* light of the large number of individuals affected, and the attendant costs of this disease to society, the Committee is concerned that insufficient resources are being devoted to finding ways to cure, prevent and more effectively treat peripheral neuropathy. To that end, the Committee strongly urges NINDS to (1) determine how much NIH is devoting to research in this area, and (2) develop a research agenda that is coordinated with work being done through other institutes. The Committee expects to receive a report on this effort at next year's hearings, (p. 122)

Action taken or to be taken

Please refer to page NINDS-36 of this document for the NINDS response to this significant items regarding peripheral neuropathy.

Item

Spina bifida - The Committee strongly encourages the NINDS to enhance research to address issues related to the outcomes of the conference and urges significant expansion of prevention and treatment of spina bifida and associated secondary conditions. The Director should be prepared to testify on efforts to advance these areas of research at the fiscal year 2006 appropriations hearing, (p. 123)

Action taken or to be taken

Please refer to page NINDS-38 of this document for the NINDS response to this significant item regarding spina bifida.

Item

Stroke - The Committee continues to regard research into the causes, cure, prevention, treatment and rehabilitation of stroke as a major concern for our Nation and urges the NIH and the NINDS to make stroke a lop priority. Stroke remains America's third most common killer, a major contributor to late-life dementia, and a major cause of permanent disability. The Committee continues to strongly support increased efforts on stroke research. The Committee is very concerned that funding for stroke research over the years has not kept pace with the scientific opportunities, the number of Americans afflicted with stroke, and the economic toll this disease imposes on our Nation. The Committee urges the NINDS to aggressively expand its research portfolio and dramatically increase resources dedicated to stroke research through all available mechanisms. The Institute is urged to expand its stroke education program, to continue to implement the long-range strategic plan for stroke research and to continue and expand innovative approaches to improve stroke diagnosis, treatment, rehabilitation, and prevention, (p. 123)

Action taken or to be taken

The NINDS is acutely aware of the burden that stroke places on the health of our nation, and has committed significant levels of funding for stroke research in the past. At present, the NJNDS is heavily invested in this field, supporting a wide variety of research from preclinical studies of the relationship of estrogen to stroke risk, to more than thirty clinical studies, such as an evaluation of noninvasive imaging techniques that can confirm the presence of arterial hardening and clogging in the brain, and an initial clinical assessment of a rehabilitation technique involving forced use of the arm affected by stroke, through restraint of the functional Jimb.

To keep pace with the evolving needs of the stroke research community, and the increasing burden of this disease, NINDS organized the Stroke Progress Review Group in 2001 and this Group issued its initial report in April 2002. Guided by the recommendations in this report, NINDS has issued several grant solicitations on critical research areas, such as cognitive impairment after stroke; the blood-brain banner; stroke prevention in minority populations; and the functional relationship between the brain and its blood system. A future grant solicitation is also planned on modulation of the immune system as a therapeutic strategy for stroke prevention. In addition to these announcements, NINDS has also explored some of the most pressing areas of stroke research through sponsorship of scientific workshops on acute stroke treatment; strokes caused by intracerebral bleeding; prevention of first strokes; and cognitive impairment following stroke. The NINDS has also planned a workshop on the link between sleep disturbances - such as sleep apnea and nocturnal heart arrhythmias - and stroke, for 2005.

In stroke education, NINDS is continuing its "Know Stroke. Know the Signs. Act in Time." campaign, with a new grassroots education program called "Know Stroke in the Community." This program, a collaboration with the Centers for Disease Control and Prevention, enlists individual "Stroke Champions" to serve as leaders in the education efforts. To date, it has already delivered stroke education messages and materials to more than 100,000 high-risk individuals.

Although these activities illustrate the aggressive implementation of the Stroke PRG, NINDS has also conducted a more systematic search for unmet research needs, by mapping its current and planned stroke research activities to the areas of need identified in the PRG. NINDS presented these findings to the SPRG leadership in January 2003, and requested their help in identifying remaining research gaps, and defining priorities for the further implementation of the report. The NINDS leadership and staff continue to explore program options to meet the needs identified at this meeting.

Authorizing Legislation

	PHS Act/ Olher Citation	U.S, Cock Citation	2005 Amount Authorized	FY 2005 Appropriation	2006 Amount Authorized	2006 Budget Estimate
Research and Investigation	Section 301	42 §241	Indefinite		Indefinite	
Disorders and Stroke	Section 41B	42§2S5b	Indefinite *J*	$1,508,110,000	Indefinite *J*	51,519,122,000
National Research Service Awards	Section 487(d)	42§288	*w*	31,338,000	*u*	31,138,000
Total. Budget Authority				1,539,448,000		1,550,260,000

•*d/* Amounts authorized by Section 301 and Title IV of the Public Health Act

b! Reauthorizing legislation will be submitted.

Appropriations History

Fiscal Year	Budget Estimate lo Congress	House Allowance	Senate Allowance	Appropriation]_[
1997	S671,148,000 2/	5725,478,000	$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)
200]	1,050,412,000 2/	1,185,767,000	1,189,425,000	1,176,482,000
Rescission				(383,000)
2002	1,35 6,448,000	1,306,321,000	1,352,055,000	1,328,188,000
Rescission				(1,522,000)
2003	1,432,305,000	1,432,305,000	1,466,005,000	1,466,005,000
Rescission				(9,529,000)
2004	1,468,926,000	1,468,326,000	1,510,926,000	1,510,776,000
Rescission				(9,569,000)
2005	1,545,623,000	1,545,623,000	1,569,100,000	1,539,448,000
Rescission				(12,675,000)
2006	1,550,260,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in thcNIH Office of AIDS Research.
3/ Excludes enacted administrative reduction of S339,000
4/ Reflects a decrease of S2,457,000 for the budget amendment for Bioterrorism.

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	59	65	65
Division of Intramural Research	393	400	400
Division of Extramural Activities	83	98	98
Total	535	563	563
FTEs supported by funds from Cooperative Research and Development Agreements	(2)	(2)	(2)

FISCAL YEAR	Average GM/GS Grade
2002	10.7
2003	11.2
2004	11.2
2005	11.3
2006	11.4

Detail of Positions

GRADE	FY 2004 Actual	FY2005 Appropriation	FY 2006 Estimate
Total - ES Positions	3	3	3
Total - ES Salary	5432,596,000	$449,414,208	S461,334,921
GM/GS-15	36	32	31
GM/GS-14	37	39	40
GM/GS-13	63	62	61
GS-12	61	60	60
GS-11	53	53	53
GS-10	6	6	6
GS-9	40	42	42
GS-8	20	21	21
GS-7	14	15	15
GS-6	4	5	5
GS-5	1	3	5
GS-4	2	2	2
GS-3	3	1	0
GS-2	0	3	4
GS-1	4	1	0
Subtotal	344	345	345
Grades established by Act of July I., 1944(42U.S.C.2O7):			
Assistant Surgeon General			
Director Grade	4	4	4
Senim Grade	2	2	3
Full Grade	2	2	1
Senior Assistant Grade			
Assistant Grade			
Subtotal	8	S	8
Ungraded	202	202	202
Total permanent positions	343	368	368
Total positions, end of year	557	558	558
Total full-time equivalent (FTE) emp1oyment,end of year	535	563	563
Average ES salary	SI 44,199,000	$149,804,736	S153,778;307
Average GM/GS grade	11.2	U.3	11.4
Average GM/GS salary	$71,513,000	$74,293,068	576,263,692