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National Institute of Neurological Disorders and Stroke

INTRODUCTION

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disease—a burden borne by every age group, by every segment of society, by people all over the world. To this end, the Institute supports and conducts research on the healthy and diseased brain, spinal cord, and peripheral nerves, in an effort to address the hundreds of disorders that afflict the nervous system.

NINDS collaborates with leading scientists in medical institutions worldwide to conduct, foster, coordinate, and guide research on the causes, prevention, diagnosis, and treatment of neurological disorders and stroke. The Institute also supports basic research in related scientific areas. In addition, NINDS provides grants-in-aid to public and private institutions and individuals in fields related to its areas of interest, including funding of research projects, program projects, and research center grants; supports individual and institutional fellowships to increase scientific expertise in neurological fields; and conducts a diversified program of intramural and collaborative research in its own laboratories and branches. International collaboration leads to new discoveries that enable NINDS to benefit from the research of other institutions and investigators around the world. International collaboration exists in many areas, including the following:

- studies involving multinational organizations;
- research grants and fellowships to foreign institutions;
- international conferences, seminars, meetings, and workshops;
- research conducted as part of the World Health Organization (WHO) collaborating centers;
- joint efforts uniting NINDS scientists and foreign colleagues; and
- research projects conducted by visiting scientists from all over the world.

International collaboration frequently allows scientists to conduct research that is not possible in the United States, such as studies focusing on outbreaks of neurological diseases or on geographic differences in disease distribution. For example, scientists can seek out and study extended families affected by neurological diseases with a genetic link. NINDS scientists continue to cooperate internationally to advance research and training in the neurological sciences.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Repair of Severed Nerve Fibers in Animal Model of Spinal Cord Injury

Traumatic injuries to the brain, spinal cord, and peripheral nerves often involve severing or crushing of axons—nerve fibers that transmit the electrochemical signals of the nervous system, which are the basis for sensory and motor activity. Such injuries disrupt axonal conductance, so that this critical cellular communication is no longer possible. They can cause severe disorders, ranging from muscle weakness to paralysis and abnormal sensation or no sensation. Interruption of life functions as a result of such injuries affects millions of persons in the United States every year, and these injuries are a leading cause of disability in both children and adults.

After interruption of axonal connections, some amount of regeneration can take place. The regrowth of axons is slow and inefficient, however, and reformation of the circuitry needed for return of normal function remains a goal of research.

NINDS grantees, collaborating with investigators from the Swiss Federal Institute of Technology and the University of Zürich, Switzerland, have taken a different approach to the problem of nerve injury. Rather than attempt to enhance regeneration, they seek to heal the damaged axons. They have developed and tested a procedure to "glue" the severed ends of the axons back together. Their in vitro technique uses calcium-free solutions of polyethylene glycol (PEG) to rapidly induce fusion of the ends of severed axons from rat sciatic nerve. Physiological measurements indicate that the resealed axons transmit action potentials. In vivo studies showed that PEG alone would fuse axons, but the natural movement of the animal disconnected the repaired nerves. To ensure a more permanent seal, the investigators incorporated PEG into a hydrogel that bound to surrounding tissues and held the axons together.

The potential to reseal or reattach injured axons, which prevents the axons from degenerating, opens a new avenue of therapy for spinal cord and peripheral nerve trauma.

Blood Test to Detect Curable, Dangerous Cause of High Blood Pressure

High blood pressure (hypertension) has many possible causes. Rarely, hypertension results from a benign tumor of the adrenal gland, a key gland that sits atop each kidney. The tumor, called pheochromocytoma, releases potent biochemicals such as adrenaline into the bloodstream. Although rare, these tumors are important in clinical medicine. Whereas most cases of hypertension require long-term treatments, surgical removal of this type of tumor can cure the hypertension. Diagnosis and surgical removal are also important because this tumor, in response to seemingly mild stressors, can secrete adrenaline or other potent related biochemicals into the bloodstream, and these catecholamines can produce catastrophic consequences such as heart attack and sudden death. None of the available blood tests have been sufficiently sensitive to detect pheochromocytoma in all patients. NINDS investigators are collaborating with a scientist from St. Radboud University Hospital, Nijmegen, the Netherlands,

to develop a method to measure, in human plasma, breakdown products of catecholamines from cells in the adrenal gland. Planned studies will attempt to elucidate specific genetic mutations that predispose persons to develop disorders associated with pheochromocytoma. Understanding how different mutations cause different tumor cell types will lead to better understanding of tumorigenesis and spur development of new and improved approaches for diagnosis and treatment of pheochromocytoma.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Collaboration continues with investigators from the Sakha Republic of Russia in research on Viliuisk encephalomyelitis in the Iakut people of Siberia. This disease is a progressive neurological disorder with a fatal outcome and is seen only among the Iakuts. The project has involved training of several Russian researchers in NINDS laboratories, as well as on-site data collection and evaluation in Siberia.

Activities With International and Multinational Organizations

NINDS serves as 1 of the 12 WHO Collaborating Centers for Research and Training in the Neurosciences. NINDS and WHO cooperate in an effort to increase the ranks of qualified neurological scientists willing to undertake highly skilled investigations in more isolated, less developed regions. The International Neurological Science Fellowship Program brings investigators from developing countries to the United States for advanced research training. These scientists then return to their own countries to pursue leadership positions in neurological research and education. In fiscal year 1999 (FY 99), NINDS supported two neurological science fellowships, to applicants from Kenya and Turkey.

Extramural Programs

NINDS supported 20 foreign research and training awards in five countries during FY 99. Additionally, numerous NINDS grants to domestic institutions incorporate foreign components. A wide range of neurological issues is being addressed, including the search for answers to key questions about the causes of neurological disorders, studies of prevention methods and potential therapies for neurological diseases, and research to identify various genes.

International Meetings

NINDS staff continue to undertake various initiatives to establish new ties and to share research information and strategies with their international colleagues. This collaborative effort facilitates pooling information and ideas, accelerates ongoing projects, and promotes interest in medical problems needing greater attention.

International conferences and workshops attended by NINDS staff include the following:

- Movement Disorder Society satellite meeting on Muscle Stiffness, Port Douglas, Australia;
- 5th International Symposium on Mucopolysaccharidoses and Related Disorders, Vienna, Austria;
- Conference on Excitatory Amino Acids, Manaus, Brazil;
- XIIth International Congress on Parkinson's Disease, Vancouver, British Columbia;
- International Dystonia Symposium, Victoria, British Columbia;
- 5th Alschul Symposium, Saskatchewan Stroke Research Center, Saskatoon;
- International Federation of Clinical Neurophysiology, Prague, Czech Republic;
- Movement Disorder Society satellite meeting on Gait Disorders, Prague, Czech Republic;
- 16th International Symposium on Cerebral Blood Flow and Metabolism, Copenhagen, Denmark;
- International Brain Edema Symposium, New Castle upon Tyne, England;
- Summer School of Mouse Pathology, Helsinki, Finland;
- 1st Biennial Kupio Stroke Symposium, Kupio, Finland;
- French Neurological Society International Congress, Paris, France;
- Symposium on Signal Transduction Pathway in the Blood–Brain Barrier, Berlin, Germany;
- International Brain Research Organization, Jerusalem, Israel;
- Conference on Genomic Views on Jewish History, Judean Hills, Israel;
- Symposium on Neuroscience of Memory and Learning, Catania, Italy;
- 6th European Network on Brain Dysmyelinating Diseases: Developmental Defects of Myelin Formulation—From Mouse Mutants to Human Diseases, Padua, Italy;
- Human Brain Activity Related to Voluntary Movement, Rome, Italy;
- 4th Annual Symposium on Advances in Stroke Management, Sardinia, Italy;
- 8th European Stroke Conference, Venice, Italy;
- 4th International Congress of Neuroendocrinology, Kitakyushu, Japan;
- International Symposium on Neural Progenitor Cells, Tokyo, Japan;
- meeting of the Japanese Society on Microcirculation, Tokyo, Japan;
- International Neuroatiology World Scientific Conference, Algarve, Portugal;
- Life Sciences Conference, Gozd Martuljek, Slovenia;
- Wenner-Gren Symposium on Volume Transmission Revisited, Stockholm, Sweden;
- International Symposium on Neural Regeneration, Pacific Grove, California;
- International Scientific Symposium on Tourette Syndrome, New York City, New York; and
- 1st International Clinical Neuroscience Symposium, Punta del Este, Uruguay.

Intramural Programs and Activities

The NINDS Division of Intramural Research consists of 11 branches (Clinical Neuroscience Program) and 11 laboratories (Basic Neuroscience Program). Additionally, there are 12 independent sections and units. The branches and laboratories host a number of international investigators. Additionally, many of the scientists in the Division engage in international research through collaboration with foreign scientists and through assignments in laboratories in other countries.

The Clinical Director, NINDS, is conducting informal collaborations with the Istituto Nazionale a Carattere Scientific, Florence, Italy, on studies of balance in older adults. He is also working with the Department of Neurology, University of Kyoto, Japan, on studies of physiology of the motor area of the cortex.

Developmental and Metabolic Neurology Branch

The Developmental and Metabolic Neurology Branch carried out a number of international research projects during FY 99.

These efforts include collaboration with scientists at the Panum Institute, Copenhagen, Denmark, to identify mutations in the gene for α-galactosidase A that is altered in patients with Fabry disease. The Division also is collaborating with researchers at the Hôpital St. Vincent de Paul, Paris, and Clermont-Ferrand University, France, in a study of genetic alterations in patients with leukodystrophies. The Division is working with investigators at Tottori University, Yonago, Japan, to identify the second gene that is mutated in patients with type C Niemann-Pick disease. Additionally, Division staff are collaborating with investigators at the National Institute of Neuroscience, Tokyo, Japan, on development of neural stem cell therapy for patients with inherited metabolic disorders.

Experimental Therapeutics Branch

In the Clinical Pharmacology Section, Experimental Therapeutics Branch, Visiting Scientists from China, Greece, Ireland, Italy, and the Netherlands are participating in studies of the pathogenesis and treatment of neurodegenerative disease. The two scientists from China are investigating the relationship of apoptotic mechanisms in dopaminergic neurons to the pathogenesis of Parkinson's disease. In a related study, a researcher from the Netherlands is studying the regulation of striatal metabotrophic receptors in relation to the production of parkinsonian symptoms. An investigator from Ireland is conducting clinical studies on several new strategies to improve cognitive function in patients with Alzheimer's disease. A neurologist from Italy has been doing research on novel approaches to neuroprotection in a primate model of Parkinson's disease. Joint research projects continue with scientists at the University of Barcelona, Spain, and the University of Göteborg, Sweden, to explore glutamatergic–dopaminergic interactions in the basal ganglia.

The Branch's Genetic Pharmacology Unit is hosting Visiting Scientists from England and Korea, who are focusing on the elucidation of pathogenetic mechanisms in neurodegenerative diseases and on the role of transcription factors and cofactors in neuronal function. Investigators in this Unit continue to collaborate with investigators at the University of Tokyo, Japan, in the search for protein–protein interactions in Huntington's disease and related disorders. In addition, a collaboration with researchers at the University of Aarhus, Denmark, was recently initiated to study the biochemical aspects of mutant proteins in Parkinson's disease.

Scientists in the Neurophysiological Pharmacology Section are continuing joint efforts with a scientist at the National Institute of Physiological Sciences, Okazaki, Japan. The goal of these studies is to develop mechanisms to quantitate the properties of the slow oscillations in electrical activity in the basal ganglia recently described by scientists in the Section.

Medical Neurology Branch

The Director of the Medical Neurology Branch (MNB) is conducting informal collaborations with the Istituto Nazionale a Carattere Scientific, Florence, Italy, on studies of balance in older adults, and with the University of Kyoto, Japan, on studies of motor cortex physiology. In addition, he is president of the international Movement Disorder Society and editor-in-chief of *Clinical Neurophysiology*, the journal of the International Federation of Clinical Neurophysiology.

Researchers from the Human Cortical Physiology Section, MNB, have collaborated with researchers from Humboldt University of Berlin, Germany, to investigate the relationship between nerve and motor reorganization and the phantom pain frequently experienced by amputees. They also are working with scientists from the University of Tübingen, Germany, in studies to evaluate the use of transcranial magnetic stimulation to enhance communicative abilities of patients with amyotrophic lateral sclerosis and in a study on recovery of motor function in stroke. The Human Cortical Physiology Section hosted scientists from Brazil, Germany, and Switzerland.

The Laryngeal and Speech Section, MNB, studies the integrated control of laryngeal functioning in normal and disordered voice, speech, and swallowing. A joint research project was conducted in FY 99 with investigators at the University of Padua, Italy. The study is examining the effects of long-term neuromuscular stimulation on plasticity of the muscle fiber bands that contain myosin, in normal and denervated thyroarytenoid laryngeal muscles. The purpose was to determine whether the normally fast type of laryngeal muscle fibers are altered after nerve injury and whether fiber type could be maintained by long-term neuromuscular stimulation. The Laryngeal and Speech Section is currently hosting three Special Volunteers—from Argentina, Brazil, and Germany, each for 1 year.

Cognitive Neuroscience Section

Scientists from the Cognitive Neuroscience Section are collaborating with scientists from the Institut des Sciences Cognitives, Centre National de la Recherche Scientifique, Lyon, France, on research designed to identify the functions of the human prefrontal cortex. In particular, these joint studies are focusing on which elements of a cognitive plan are stored in the prefrontal cortex and on the role of the prefrontal cortex in modulating mechanisms of reward and punishment. Work continues with scientists from the University of Pisa, Italy, on functional neuroimaging research to elucidate the role of the prefrontal cortex in modulating aggressive human behavior. Researchers from this Section, together with researchers from the University of Modena Policlinico, Italy, are performing behavioral research and neuroimaging to determine the role of the prefrontal cortex in estimating the passage of elapsed time, the effects of implanted stimulators on cognitive symptoms of Parkinson's disease, and the effects of prefrontal cortical lesions on social behavior. Investigators from the Section are working with investigators from the Hospital de Galdakao, Spain, on studies to elucidate the mechanisms by which the prefrontal cortex mediates learning of simple visuomotor sequences.

In the Cognitive Neuroscience Section, Visiting Scientists from Bulgaria, Canada, Croatia, France, and Italy are performing research in diverse areas related to cognition. These areas include reasoning, planning, time perception, aggression, attention, mathematics, memory, and neuroplasticity.

Neuroepidemiology Branch

A geneticist from the University of Western Australia, Perth, has been working with scientists in the Neuroepidemiology Branch on the International Collaborative Study of Childhood Neurologic Morbidity in Multi-

ple Births. The scientists collected data from population-based studies in Australia, England, and the United States. These data, containing information on 1.2 million births, have been examined to determine the relationship between the birth of twins and neurological disability or mortality of the offspring, as well as the mechanisms involved.

Stroke Branch

The Stroke Branch hosts in its laboratories scientists from various countries, including China, Germany, Japan, and Russia. These scientists are studying the mechanisms responsible for development of tolerance to ischemia, which is the interruption in blood flow and subsequent oxygen deprivation that occurs in stroke. Another project studies the mechanisms by which antibody therapy during acute brain ischemia can lead to tissue damage as a deleterious side effect. A study is being performed to address the mechanisms that regulate hibernation—a state of natural tolerance to ischemia. Two other international collaborations involve looking at strategies that prevent stroke in stroke-prone rats and the mechanisms that convert an asymptomatic carotid atherosclerotic plaque to a symptomatic plaque that causes transient ischemic attacks or strokes.

Stroke Branch staff are collaborating with a scientist from Hebrew University, Hadassah Medical School, Jerusalem, Israel, on mechanisms of cytotoxicity in culture systems for primary brain cells.

The Clinical Stroke Research Unit, Stroke Branch, is providing funding and laboratory support to a Fogarty International Research Fellow from Georgia to collaborate in a study on the effects of inflammatory cells in the progression and activation of atherosclerotic disease. The research goals are to identify potential environmental and endogenous factors that cause patients to have an increased risk of stroke.

Laboratory of Adaptive Systems

The Behavioral Neuroscience Unit, Laboratory of Adaptive Systems, has a number of ongoing international collaborations designed to identify the neural substrates of learning and memory. Researchers use both animals and humans to investigate classical conditioning. The first study, designed to examine differential gene expression of specific brain areas after learning, is being performed with the Institute of Bioimaging and Pathophysiology of Central Nervous System, Catania, Italy. The second study, involving kinematic, time-domain and frequency-domain analyses of eyelid responses in the rabbit, is being conducted with the University of Seville, Spain. These experiments are designed to determine the basic mechanisms controlling a simple reflex response, to increase understanding of the pathways that underlie learning in the rabbit. The third study, an analysis of human functional imaging data collected during experiments on learning and memory, is being carried out with the Rotman Research Center, University of Toronto, Ontario, and the University of Bern, Switzerland. These experiments map normal brain activity during human learning and memory.

Laboratory of Central Nervous System Studies

The Chief, Laboratory of Central Nervous System Studies, has collaborated with an investigator at St. Mary's Hospital, London, England, on human Creutzfeldt-Jakob disease and kuru. He also has ongoing projects with scientists at the University of Milan, Italy, and with a wide variety of physicians throughout Asia, Europe, and the South Pacific. He continues to serve as the senior consultant to the Director General, WHO, on emerging diseases and transmissible spongiform encephalopathies and also is a member of the Task Force on Bovine Spongiform Encephalopathy to the government of Argentina. This year he prepared a syllabus for WHO on "Strengthening Diagnosis and Surveillance of Creutzfeldt-Jakob Disease."

Laboratory of Molecular Biology

In FY 99, work performed by a collaboration between the Laboratory of Molecular Biology and the University of Bonn, Germany, attracted a great deal of attention. This study, published in *Science*, showed that oligodendrocytes could be efficiently generated from embryonic stem cells. The work was notable because it demonstrated that these cells can be used as a single source of the many cell types found in the body. In this case, oligodendrocytes were generated from the embryonic stem cells, and grafting experiments showed that the oligodendrocytes formed compact myelin in an animal model of human disease. This work suggests that new cell therapies may be possible for diseases such as multiple sclerosis that involve demyelination of nerves.

The Laboratory of Molecular Biology has hosted scientists from Chile, China, France, India, Israel, Korea, Poland, Spain, and Switzerland.

Laboratory of Molecular Medicine and Neuroscience

The Laboratory of Molecular Medicine and Neuroscience (LMMN) focuses much of its experimental investigations on human viral infections in the central nervous system (CNS). Emphasis is placed on neurotropic viruses that cause either encephalopathy or demyelination in the immune-compromised host. Infection of the CNS with human immunodeficiency virus type 1 (HIV-1) is one of the leading causes of disease in the brain, as is the human JCV polyomavirus, the etiologic agent for progressive multifocal leukoencephalopathy. Research on these viruses and the CNS diseases they cause involves basic and clinical studies that require extensive collaboration with laboratories worldwide.

Investigators in the Molecular Medicine and Virology Section study the host range of HIV-1 strains isolated from brain tissue of patients with acquired immunodeficiency syndrome (AIDS). With investigators at San Raffaele Institute, Milan, Italy, and Karolinska Institute, Stockholm, Sweden, they have found HIV-1 isolates that directly infect the numerous glial cells in the brain. Initiation of infection does not require the specific receptor or coreceptors necessary for HIV-1 infection in lymphoid cells. This observation has important implications for therapy, because attempts to block use of the chemokine receptors to limit HIV-1 infection would not be effective in the brain. Also, HIV-1 infection in the brain can remain latent in glial cells, principally the astrocyte, and can be reactivated in the presence of proinflammatory cytokines. Two of these cytokines are found in the brains of AIDS patients with dementia. If HIV-1 resides in the brain in a latent state, then the brain becomes a reservoir for synthesis of virus, which might repopulate peripheral tissues. Investigators at San Raffaele Institute, Karolinska Institute, and LMMN continue to perform research in this area and

to share new HIV-1 isolates from unique patient populations with neurological consequences of HIV-1 infection.

LMMN also collaborates with the Immunology Laboratory at the Orthopedic Institute, Bologna, Italy. That laboratory cultures chondrocytes and bone marrow from patients with inflammatory diseases. LMMN investigators joined the Bologna investigators to establish permanent cell lines from human chrondrocytes, by insertion of viral immortalizing genes into cultures of primary chrondrocytes. These cell lines will be very helpful in studies of the pathogenic processes of inflammation that occur in bone diseases and nervous system inflammation.

The principal investigators in LMMN have also cochaired a number of conferences, including the 2nd International Neurovirology Conference, which was part of the Gordon Conference series held in New London, New Hampshire, in June 1999. Members of the Laboratory have participated in international meetings on demyelination, in Milan, Italy, and on gene therapy for neurodegenerative diseases, in Lund, Sweden. They have also helped to organize a conference on the neuroscience of HIV-1 infection, to be held in Edinburgh, Scotland, in June 2000. The Chief of LMMN is the Chair of the International Viral Taxonomy Committee, which has been organized to define polyomavirus as distinct from papillomavirus, with which it had been grouped. Research has now verified that these viruses constitute different viral families.

Laboratory of Neurophysiology

Scientists from the Laboratory of Neurophysiology have worked with an investigator from the University of Vienna, Austria, to examine dopamine modulation of response to light in the distal retina of the cat and the rabbit.

Laboratory of Neural Control

The Laboratory of Neural Control (LNLC) regularly hosts junior and senior scientists from other countries. During FY 99, scientists from Canada, China, France, Japan, and Ukraine worked in LNLC. Senior investigators in the Laboratory have a number of ongoing joint projects with scientists in several countries, to determine spinal cord and brain stem structure and function, with emphasis on systems of neurons that generate rhythmic behaviors. Much of this work focuses on the rodent CNS, which has become a major model system for neuroscience research. The goal of this work is to elucidate the autonomous mechanisms in the brain stem and spinal cord that generate rhythmic breathing and locomotion. Increased understanding of these mechanisms is critical in efforts to prevent problems such as sudden infant death syndrome and to improve the quality of life for patients with spinal cord injury.

Researchers at LNLC are collaborating with a colleague at the University of Manitoba, Winnipeg, to develop an accessible tissue culture system that will permit study of the neural system that generates spontaneous respiratory movements. Preliminary results have been very encouraging. Such an in vitro system would greatly facilitate understanding of the basic mechanisms that produce breathing movements and the abnormalities that occur during human development.

In another cooperative effort, LNLC investigators and a colleague at the University of Newcastle upon Tyne, England, are investigating the mechanisms that produce spontaneous waves of activity in neurons in the retina of the chick embryo. These waves are thought to be critical for the formation of proper connections between retinal nerve cells and between these cells and their targets in the brain.

LNLC scientists also are working with colleagues at Hebrew University, Hadassah Medical School, Jerusalem, on the development of connections between the motor cortex in the rat brain and targets in the spinal cord. This research has been supported in part by the U.S.-Israel Binational Science Foundation—a key source of financial support for collaborative research with Israeli scientists.

NIH Visiting Program

During FY 99, the NINDS Division of Intramural Research hosted the following international researchers: 65 Visiting Fellows, 20 Research Fellows, 14 Clinical Fellows, 13 Visiting Associates, and 9 Visiting Scientists.