# XX.
# 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 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 Branches and Laboratories. 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

### Chemokines in Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disease that usually strikes in the early adult years. The immune cells of persons with MS cause inflammation in the brain and spinal cord and destroy the myelin that ensheathes nerve fibers and is essential for reliable conduction of high-speed nerve impulses. Despite new therapies that can slow the progression of MS, treatment for the more than 250,000 people in the United States with this disorder remains unsatisfactory.

An international collaborative effort led by NINDS grantees has now identified certain members of the chemokine family of chemical signaling molecules that are critical in MS. Chemokines attract immune cells to tissue and provoke inflammation. The levels of two specific chemokines are increased in the cerebrospinal fluid of patients during acute MS attacks but not in patients with brain inflammation from other causes. Identifying the chemokine receptors (detector molecules) on the attacking immune cells would further support the hypothesis that signals from these two chemokines are critical to the disease process in MS.

Research on chemokines has proven fruitful, because they are especially good targets for developing potent and precise drugs and because they act specifically on various types of immune cells. The finding that certain receptors and chemokines are highly expressed in the cells and tissues of the brain in patients with MS provides a first step toward the rational use of these agents in clinical trials. Much more research is needed, however, to elucidate the precise functions of these chemokines and receptors in MS.

### Isolation, Purification, and Multiplication of Adult Neural Stem Cells

Stem cells can reproduce themselves and can form more specialized cell types. Embryonic stem cells give rise to all cell types of the body, but stem cells found in the adult generally have a narrower range of developmental fates. Research is needed to learn how stem cells in adults can be coaxed to give rise to more diverse cell types.

In recent years, scientists have demonstrated, surprisingly, that new nerve cells can arise in the adult human brain. This finding indicates that some types of stem cells are probably present in adults. However, studies to characterize the capabilities of the proliferative cells and the signals that control them require methods to isolate, purify, and multiply these cells. In fiscal year 2000 (FY 00), scientists reached this goal by using brain tissue that had been removed in therapeutic surgery. The results of these studies, conducted by several international groups in collaboration with NINDS-supported investigators, suggest that the adult human brain harbors a complex population of stem cells that can give rise to nerve and supportive glial cells under appropriate culture conditions.

These findings are an important step toward better understanding of the potential of adult neural stem cells and development of therapies using stem cells. The wide array of diseases for which stem cell therapies seem plausible arise from the remarkable versatility of these cells. Replacing lost nerve and glial cells, releasing growth factors, providing missing enzymes, and bridging

physical obstacles to regeneration are just a sampling of the possibilities.

### Strategy for Gene Therapy for Parkinson's Disease

Parkinson's disease usually progresses slowly, a result of the death of nerve cells in the substantia nigra of the brain; these nerve cells produce the neurotransmitter dopamine. Several years ago, scientists isolated glial cell line–derived neurotrophic factor (GDNF), which promotes survival of dopamine cells. Short-term experiments in animal models of Parkinson's disease reinforced the hypothesis that GDNF might protect dopamine neurons, but this goal has been thwarted by the difficulties in providing sustained delivery of GDNF through the blood–brain barrier. NINDS grantees at Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois, collaborating with scientists from the French National Institutes of Health and Research (INSERM), Paris, France, and Lausanne University Medical School and the University of Geneva, Switzerland, have now adapted a lentivirus to carry the gene for GDNF into brain cells with control signals that prompt cells to produce GDNF. In nonhuman primate models of Parkinson's disease, the lentivirus gene therapy reduced degeneration of dopamine cells and improved control of movement. From a broader perspective, these findings highlight the potential of gene therapy for neurological diseases that are not caused by defective genes (e.g., most cases of Parkinson's disease).

### Understanding Narcolepsy

Narcolepsy is a serious brain disorder that affects sleep in a dramatic way. Symptoms include sudden occurrences of daytime sleep, a frightening inability to move shortly after awakening or dozing off, and dramatic episodes of muscle weakness called cataplexy. In 1999, scientists supported by NINDS discovered a defective gene that causes narcolepsy in dogs, one of the few animals that exhibit this disorder. The gene carries the instructions for making a receptor by which nerve cells respond to hypocretin, a brain-signaling chemical. NINDS-supported investigators, working with scientists from Charles University, Prague, Czech Republic, Leiden University Medical Center, the Netherlands, and Belle-idée, Chene Bourg, Geneva, Switzerland, were guided by the findings in animal studies to examine the hypocretin system in humans. They have shown that, like the animal models, most persons with narcolepsy have defects in the hypocretin signal system. Rather than loss of receptors, persons with narcolepsy have abnormally low levels of the hypocretin signal in the brain. Apparently, the nerve cells that normally produce hypocretin either die or stop producing this substance. Supplying hypocretin or drugs that mimic its actions may help in prevention or treatment of this disease.

## SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

### 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 countries and emerging democracies. The International Neurological Science Fellowship Program brings investigators from these areas to the United States for advanced research training. The scientists then return to their countries to pursue leadership positions in neurological research and education. In FY 00, NINDS supported three neurological science fellowships, to investigators from the Czech Republic, Egypt, and Russia.

### Memorandum of Understanding With Japanese Institution

In November 2000, the NINDS Director and the director general of the Okazaki National Research Institutes, Japan, signed a Memorandum of Understanding for an exchange program in the neurosciences. The Brain Research Cooperative Program will facilitate collaborative neuroscience research and training between the United States and Japan.

### Neurological Complications of AIDS

Several European academic centers—located in Paris, France, Amsterdam, the Netherlands, and Edinburgh, Scotland—were among the first to recognize the neurological complications of human immunodeficiency virus type 1 (HIV-1). They supported clinical studies that led the way in evaluating the extent of HIV-1 infection in the brain. These centers have maintained joint research efforts in the basic sciences and in clinical studies, related to acquired immunodeficiency syndrome (AIDS), with institutions in Central and Western Africa, Asia, and India. There is increasing understanding of the effectiveness of highly active antiretroviral therapy (HAART) and treatment of non-neurological complications in patients with AIDS in the United States. NINDS staff have recommended increased attention to similar efforts to provide treatment for HIV-1–infected persons in developing countries, where the epidemic is not in control. Little is known about the extent and severity of nervous system involvement associated with HIV-1 in such countries, even with international planning to help provide treatment for AIDS.

NINDS has convened an international consortium of experienced AIDS researchers in the basic sciences and clinical studies to examine this problem in greater detail, especially in the areas of neurology, pediatrics, neuropathology, and neurovirology. Studies involving diverse patient populations who have complex, multifactorial disease processes require a well-organized group effort. The consortium will address issues such as obtaining epidemiologic information on AIDS-associated neurological disease in both adults and children. Viral strains present in the central nervous system will be compared with those found in the blood and the lymphatic system. Additionally, the differences in viral strains (clades) found in specific geographic areas will be examined for their role in neurological disease associated with human immunodeficiency virus (HIV). It may be possible to develop novel treatment strategies tailored to an identifiable population. The international consortium will provide leadership for this multinational effort.

### Extramural Programs

NINDS supported 21 foreign grants and fellowships during FY 00. In addition, 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 establish new ties and to share research information and strategies with international colleagues. These collaborative efforts facilitate the pooling of information and ideas, accelerate ongoing projects, and promote interest in medical problems that need greater attention.

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

- 9th European Stroke Conference, Vienna, Austria;
- 35th Meeting of the Canadian Congress of Neurological Sciences, Ottawa, Ontario;
- Rotman Research Institute Meeting on the Human Frontal Lobes, Toronto, Ontario;
- 6th Nerve Growth Factor and Related Molecules Conference, Montreal, Quebec;
- 1st Latin American Congress on Epilepsy, Santiago, Chile;
- Shanghai International Workshop on Functional Neurosurgery, PET (positron emission tomography), and MRI (magnetic resonance imaging), Shanghai, China;
- Joint Meeting of the British Pediatric Surveillance Unit and the Royal College of Physicians of Edinburgh (Scotland), London, England;
- 3rd Cologne PET Symposium, Germany;
- Annual Meeting of the International Bioelectromagnetic Society, Munich, Germany;
- 3rd World Congress on Stress, Dublin, Ireland;
- Meeting of the Society of Internal Medicine, Kfar Hamacabiah, Israel;
- Myelin Gordon Conference, Il Cioco, Italy;
- XVIIth International Pigment Cell Conference, Nagoya, Japan;
- Annual Meeting of the Mexican National Institute of Psychiatry, Mexico City, Mexico;
- Glial Cell Function in Health and Disease, Barcelona, Spain; and
- Arolla Workshop on Signaling During Development, Switzerland.

### Intramural Programs and Activities

The NINDS Division of Intramural Research consists of 11 branches (Clinical Neuroscience Program) and 10 laboratories (Basic Neuroscience Program). Additionally, there are 14 independent Sections and Units. The Branches, Laboratories, and Sections 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.

#### Developmental and Metabolic Neurology Branch

The Developmental and Metabolic Neurology Branch carried out a number of international research projects during FY 00. These efforts include collaboration with scientists at Hôpital St. Vincent de Paul, Paris, and Clermont-Ferrand University, France, to investigate genetic alterations in patients with leukodystrophies. In addition, Branch scientists are working with investigators at Hôpital European Georges Pompidou, Paris, to identify novel mutations in children with type 3 Gaucher disease. They are also cooperating with investigators at the National Institute of Neuroscience, Tokyo, Japan, to develop neural stem cell therapy for patients with inherited metabolic disorders.

#### Experimental Therapeutics Branch

In FY 00, the Clinical Pharmacology Section, Experimental Therapeutics Branch, hosted scientists from China, Ireland, Italy, and the Netherlands who are participating in studies of the pathogenesis and treatment of neurodegenerative disease. Areas under investigation by the visiting scientists are programmed cell death (apoptosis) and pathogenesis of dopamine-producing neurons in Parkinson's disease and progressive supranuclear palsy, neuroprotection in a primate model of Parkinson's disease, and strategies for replacement of neurotransmitters to improve cognitive function in patients with Alzheimer's disease. In addition, the staff of the Clinical Pharmacology Section are collaborating on a project with investigators at the University of Barcelona, Spain.

In the Branch's Genetic Pharmacology Unit, visiting scientists from Korea are focusing on the elucidation of pathogenetic mechanisms in Parkinson's disease and on the role of transcription factors and cofactors in neuronal function. Investigators in this Unit continue to work with scientists at the University of Tokyo, Japan, in the search for protein–protein interactions in Huntington's disease and related disorders. Scientists in the Unit also continue to cooperate with scientists at the University of Aarhus, Denmark, to study the biochemical aspects of mutant proteins in Parkinson's disease, and collaborations with scientists at Silla University, Pusan, Korea, are focusing on mechanisms that control transcription.

#### Neuroepidemiology Branch

For several years, the Neuroepidemiology Branch has worked with the Western Australian Research Institute for Child Health, Perth, and a geneticist from the University of Western Australia, Perth, on the International Collaborative Study of Childhood Neurologic Morbidity in Multiple Births. Data sets from population-based studies in Australia, England, Sweden, and the United States are being examined to determine the relationship between neurological disability in multiple births and its mechanisms.

#### Stroke Branch

In its laboratories, the Stroke Branch hosts scientists from various countries, including China, France, 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. One study addresses the mechanisms that regulate hibernation, a state of natural tolerance to ischemia. Two other projects are exploring the mechanisms that convert an asymptomatic carotid atherosclerotic plaque to a symptomatic plaque that causes transient ischemic attacks or strokes and strategies that prevent stroke in stroke-prone rats, a study that will be carried into clinical trials. In addition, the staff of the Stroke Branch are collaborating with a scientist from Hebrew University, Hadassah Medical School, Jerusalem, Israel, on mechanisms of cytotoxicity in primary brain culture systems.

The Clinical Stroke Research Unit, Stroke Branch, is providing funding and laboratory support for an international Fogarty Fellow from Georgia to collaborate in studies examining the role of the immune system in the progression and activation of carotid atherosclerotic plaques. The aim of the study is to examine immune response to potential

environmental and endogenous factors that can cause patients to have an increased risk of stroke due to plaque in the carotid artery. The study hypothesizes that exposure of atherosclerotic plaque to infectious agents, endogenous proteins, or both stimulates the activation of T lymphocytes that are resident in the plaque, causing a rapid escalation of intraplaque inflammation. This inflammatory response may result in clot formation on the inner lining of the blood vessel, leading to increased risk for thromboembolic stroke. To test the hypothesis, research in FY 00 has focused on comparison of expression of T-lymphocyte subtypes in atherosclerotic plaques of patients who have had a stroke or a ministroke and in plaques of those who have no symptoms in the presence of infectious organisms. The findings supported the hypothesis that infection may be one of the triggers for the activation of atherosclerotic plaque, leading to increased risk for stroke. These results have broad relevance, because atherothrombotic stroke is a significant health issue both in the United States and in Europe. NIH support and collaborative efforts with members of the NIH community are critical to these studies. This research on the role of the immune system in atherosclerosis will continue to be important.

### Laboratory of Developmental Neurogenetics

Scientists in the Laboratory of Developmental Neurogenetics have collaborated with investigators at the Research Institute, Hospital for Sick Children, Toronto, on eye development studies; with staff from the Medical Research Council, London, England, on the analysis of a developmental mouse mutation; and with scientists from the University of Iceland, Reykjavik, on the analysis of a mutation that causes hearing deficiency. Additionally, visiting foreign scientists in the Laboratory are studying the role of signaling molecules, patterns of gene expression, and transcription factors on oligodendrocyte nerve cells.

### Clinical Neurocardiology Section

The Clinical Neurocardiology Section hosted Special Volunteers from England and the Netherlands who are assisting in a clinical protocol to measure the body's stress system by using PET scanning. The locations and function of sympathetic nerves in the various organs of the body are visualized to determine the effects of various drugs and stressors on the system and to suggest how the activity of the system may change in diseases.

Scientists from the Netherlands and Sweden worked in the Section's laboratories on a study of blood sampling for neurochemical and genetic testing. This study sampled blood from healthy volunteers and from patients with diseases known or suspected to involve catecholamines. The blood will be used to establish normal values for plasma levels of catecholamines and related neurochemicals; to test for abnormal neurochemical patterns in patients; and to establish a bank of DNA from healthy volunteers and patients, to be used in future studies on possible alterations of catecholamine-related genes. The Clinical Neurocardiology Section collaborated with foreign scientists to produce a number of publications in FY 00.

### Cognitive Neuroscience Section

Investigators from the Cognitive Neuroscience Section are collaborating with scientists from the CNRS Institut des Sciences Cognitives, Lyon, France, on research designed to identify the functions of the human prefrontal cortex. These studies are focusing on which elements of a cognitive plan are stored in the prefrontal cortex and on its role in modulating reward and punishment mechanisms. Joint research continues with scientists from the University of Pisa, Italy, on functional neuroimaging designed to elucidate the contribution of the prefrontal cortex in modulation of aggressive human behavior. Investigators from this Section are also working with scientists from the University of Modena Policlinico, Italy, on behavioral and neuroimaging research designed to determine the role of the prefrontal cortex in estimating the passage of elapsed time, the effects of implanted stimulators on cognitive symptoms in patients with Parkinson's disease, and the effects of prefrontal cortical lesions on social behavior. Additionally, they are working with scientists from the Hospital de Galdakao, Spain, to explore how the prefrontal cortex mediates the learning of simple visuomotor sequences. Research has begun with scientists from the Hospital Barra D'Or, Rio de Janeiro, Brazil, on the mechanisms of moral decision making.

Visiting scientists from Bulgaria, Canada, Croatia, France, Italy, and the United Kingdom are performing research in diverse areas related to cognition, including reasoning, planning, time perception, aggression, attention, mathematics, memory, and neuroplasticity.

### Laryngeal and Speech Section

The Laryngeal and Speech Section studies the integrated control of laryngeal functioning in normal and disordered voice, speech, and swallowing.

During FY 00, the Section hosted five scientists from other countries. A volunteer from Argentina studied speech perception in children and adults with a familial phonological processing disorder. A volunteer from Brazil examined changes in laryngeal motor control after sensory nerve injury in an animal model of adult-onset voice disorders. A volunteer from Germany studied the effects of neuromuscular stimulation for control of laryngeal movement, to develop a new treatment for chronic dysphagia after stroke. An otolaryngologist from Japan started a study of changes in brain stem neuronal function in response to laryngeal inflammation. Finally, an otolaryngologist from Korea began a study of the sensory pathways involved in laryngeal protective reflex responses such as coughing.

### Neurotoxicology Section

In FY 00, the Neurotoxicology Section investigated the molecular epidemiology of JC virus, the cause of a devastating neurological disease known as progressive multifocal leukoencephalopathy in Europe. This study involved collaboration of Section scientists with scientists in four European countries (Germany, Hungary, Poland, and Spain). Particularly involved were scientists from the University of Freiburg, Germany, and the University of Barcelona, Spain. The scientists found that the virus is ubiquitously distributed, and they are now searching for variants that may differ in their ability to cause neurological disease.

### Neurotrophic Factors Section

Investigators from the Neurotrophic Factors Section have worked with investigators from the University of Göteborg, Sweden. A grad-

uate student from this institution has worked in the Neurotrophic Factors Section on a project involving knockout mice, to determine genes that prevent astrocytes from forming glial scars in response to central nervous system injury. Other visiting scientists are working on characterization of reactive astrocytes that are produced in a rat animal model of Parkinson's disease.

**NIH Visiting Program**

During FY 00, the NINDS Division of Intramural Research hosted 26 Research Fellows and 10 Clinical Fellows under the NIH Visiting Program.