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DEPT OF HEALTH & HUMAN SERVICES

**Subcommittee on Brain and
Behavioral Sciences**

- Committee on Life Sciences and Health
- Federal Coordinating Council for
Science, Engineering, and Technology
- Office of Science and Technology Policy

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Silvio O. Conte

1921 - 1991

This report resulted directly from the foresight and leadership of Representative Silvio O. Conte of Massachusetts. As the ranking minority member of the House Appropriations Committee, Mr. Conte was an enthusiastic supporter of biomedical research. Recognizing the accomplishments of neuroscience research and the growing potential for new methods to treat and prevent brain and behavioral disorders, Mr. Conte introduced legislation to declare the 1990s the Decade of the Brain. As a result of Mr. Conte's vision, public, congressional, and international interest in brain and behavioral research continues to grow.

We respectfully recognize Mr. Conte's dedication and contribution to improving the health and well-being of Americans in the Decade of the Brain and beyond.

Foreword

The brain is the most sensitive and complicated part of the human body; it is the seat of intelligence, interpreter of senses and controller of movement. Viewed as mysterious and incomprehensible in the past, the human brain is at last yielding up its secrets, giving us insight into how it works and what goes wrong when it is injured or diseased.

We have learned more about the brain and the nervous system during the last 10 years than throughout all of history, and progress during the Decade of the Brain promises to be quite spectacular. The technological revolution occurring in the brain sciences, including the development of powerful microscopes and sophisticated brain imaging devices, new and better animal models, and major advances in the study of genetics, has brought us to a threshold as important and as promising as the first launch into space. For the first time, scientists can view, study and treat the intact, functioning brain, which previously has been inaccessible.

The challenge is enormous: more than 50 million Americans are affected each year by brain disorders that range from stroke, brain and spinal cord injury and neurogenetic diseases, to Alzheimer's disease, schizophrenia, alcoholism and drug abuse. One in four Americans at some point in life will suffer a brain-related disorder. In the United States, brain-related disorders cause more people to be hospitalized than any other major disease group, including cardiovascular disease or cancer. Treatment, rehabilitation and related consequences of brain diseases cost America an estimated \$305 billion each year.

Advancing our capability to understand and effectively treat the many brain and behavioral disorders, whether genetic or environmental in origin, will improve every aspect of our nation's well-being. Many brain disorders could be prevented, cured or alleviated inexpensively if research opportunities were fully exploited. Further progress depends on a broad-based research effort using the newly developed technologies that have already given promise of success.

Recent advances in our understanding of the nervous system are also stimulating the development of new high technologies in this country. A major emphasis on basic brain sciences during the Decade of the Brain will accelerate this effort.

This report presents highlights of the most promising areas of brain and behavioral sciences research being carried out by the Federal agencies responsible for directing, conducting and supporting such research. Each chapter includes recent significant accomplishments as well as future plans and potential benefits.

The 22 separate Federal member organizations represented in this report are committing a substantial portion of their resources to the brain and behavioral sciences. This interagency inventory allows these groups to coordinate their research, promote collaboration among their scientists, program managers and the institutions they support, and stimulate the integration of their research and development in advanced, high-priority, enabling technologies, such as imaging techniques and genetic studies.

Designation of the 1990s as the Decade of the Brain recognizes both the tremendous opportunities presented by recent and anticipated advances in brain research and the enormous costs that disorders of the brain exact in human suffering, financial sacrifice and national resources. The compelling message of the Decade of the Brain is that the brain and behavioral sciences are rich with the scientific means and opportunities to expand our knowledge, produce new, high-level technological innovations for industry, and reduce the personal and financial burden of brain-related disorders for the nation. The decade of the 1990s is the ideal time to take maximal advantage of these opportunities.

D. Allan Bromley
Director
Office of Science and Technology Policy

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Background to the U.S. Decade of the Brain

■ Legislative History

Pursuant to the House Committee on Appropriations report on the fiscal year 1988 budget for the Department of Health and Human Services (DHHS), the National Advisory Neurological Disorders and Stroke Council and the National Advisory Mental Health Council were asked to prepare reports to Congress setting forth neurosciences priorities and programs. The purpose of the reports was to assist the committee in initiating its commitment to the next 10 years as the Decade of the Brain.

On March 8, 1989 the late Congressman Silvio O. Conte introduced H.J.Res. 174, to designate the decade beginning January 1, 1990 as the Decade of the Brain. A companion bill (S.J.Res. 173) was introduced by Senator Donald W. Riegle, Jr. H.J.Res. 174 passed the House on June 29 and the Senate on July 13.

The President signed the bill on July 25, 1989 and it became Public Law No. 101-58. On July 17, 1990, President Bush issued a Decade of the Brain Proclamation, calling upon all public officials and the people of the United States to observe the decade with appropriate programs and activities.

■ Office of Science and Technology Policy

Congress has requested that the Office of Science and Technology Policy (OSTP) lead Federal activities in coordinating the scientific effort for the Decade of the Brain (House Report 101-450). In response, the OSTP's Federal Coordinating Council for Science, Engineering, and Technology (FCCSET) Committee on Life Sciences and Health has formed a Subcommittee on Brain and Behavioral Sciences.

This Subcommittee is composed of representatives from the following Federal departments and agencies:

Agency for International Development
Department of Agriculture
Department of Commerce
Department of Defense
Department of Education
Department of Energy
Department of Health and Human Services

Department of State
Department of Veterans Affairs
Environmental Protection Agency
National Aeronautics and Space Administration
National Science Foundation
Office of Management and Budget
Office of Science and Technology Policy

The FCCSET Committee on Life Sciences and Health, chaired by DHHS Assistant Secretary for Health, James O. Mason, M.D., Dr.P.H., has charged this Subcommittee with:

- designing a plan to integrate research efforts,
- monitoring scientific progress in the field,
- developing mechanisms for international collaboration,
- reviewing national and international policy issues,
- translating research discoveries into treatment and prevention applications, and
- strengthening disease prevention strategies through the understanding of high-risk behaviors.

Executive Summary

The U.S. Decade of the Brain offers scientists throughout the Federal Government a unique opportunity to advance and apply scientific knowledge about the brain and nervous system. During the next 10 years, scientists hope to maximize human potential through studies of human behavior, senses and communication, learning and memory, genetic, chemical alterations, and environmental interactions. Progress in these areas should lead to reductions in mortality from brain and nervous system disorders and to improvements in the quality of life.

Several developments have converged to make the goals of the Decade of the Brain attainable in the 1990s:

- The science essential to an understanding of the brain has matured dramatically in the past few decades, permitting a greater transfer of basic laboratory knowledge to practical applications.
- The methodologies and research tools to examine the processes at work in the healthy and the unhealthy brain are rapidly maturing.
- Medical, research and other professional institutions and organizations in the United States and countries around the world are strongly committed to advancing our understanding of the human brain.

This report identifies nine research areas that could form the basis of an integrated program in the brain and behavioral sciences. A chart summarizing the Federal activities in these nine areas may be found at the back of the report. In addition, three areas that span the nine research areas—basic research, technology and international activities—are considered.

■ Cross-Cutting Program Areas

Basic Research. Present knowledge about the brain and nervous system is built upon the foundation of basic research. Many examples of important basic research questions on which work must continue can be cited. These include: how nerves communicate normally between and among themselves; how genes determine normal nerve pathways, networks and neural development; and how normal body chemicals such as transmitters and hormones affect brain function. The new Federal initiative to sequence the human genome is another example of research that will yield basic information that can be applied to under-

standing the human brain and behavior. Providing a full description of the human genetic profile is a first step toward creating individualized prevention and treatment programs for those at risk for genetic disorders. Other important applications of this research include development of new technologies in automation, microscopy and robotics, tools that will aid studies aimed at understanding the molecular function of the brain. Continued use of animals for scientific studies will be critical for basic research.

Technology. Advances in neuroscience technology, including sophisticated computers, modeling techniques and brain imaging technology, have dramatically boosted scientists' capacity to understand brain function and dysfunction. These tools allow scientists to capture, store and analyze biological data, and to create simulations of brain function. There is great promise that molecular genetics studies of the brain will result in new methods of detecting and potentially correcting many currently untreatable genetically based diseases of the brain and central nervous system. In addition to furthering current knowledge of human disease, research in these areas is likely to revolutionize vital national industries such as computer and solid state silicon chip industries.

International Activities. Science is by nature international, and many of the advances in brain research in the coming decade will result from work conducted in scientific centers around the world. Scientists from the United States are taking advantage of the worldwide interest in the brain by joining in a number of international collaborative research projects, including studies on Alzheimer's disease, cataracts and the molecular biology of mental illness.

■ Drugs and the Brain/Addiction

Drawing on research generated by the Decade of the Brain, scientists hope to find solutions to the growing national tragedy of drug and alcohol abuse. Alarming numbers of teenagers and women of child-bearing age use illicit drugs regularly, and each year thousands of emergency room visits and deaths are caused by drug abuse. Alcohol abuse and alcoholism are factors in half of all traffic deaths, and fetal alcohol syndrome is a leading cause of mental retardation. The health costs incurred by drug and alcohol abuse and their consequences total nearly \$150 billion a year. Research efforts are providing the framework for understanding the profound effect that drugs of abuse have on normal brain function, and progress is being made on revealing the genetic and biochemical aspects of addiction.

■ Aging and the Human Brain

A steady increase in the incidence of degenerative brain disorders such as Alzheimer's and Parkinson's diseases has accompanied the upward shift in the U.S. age distribution. Our society now spends well over \$90 billion annually on the care of people with dementia, and this figure will almost certainly continue to rise. Current research priorities include identifying and understanding the causes of dementia and the pathological changes that occur in the brains of individuals with these disorders, developing accurate diagnoses, and finding treatments for brain disorders of the elderly.

■ Human Behavior and Mental Disorders

Mental and behavioral disorders affect millions of American children and adults, and have enormous economic and social consequences for our nation. Using the new research technologies available only in the past decade, scientists are now beginning to gain insight into such devastating diseases as schizophrenia. Investigators also continue to develop effective treatments for depressive disorders and other severe mental illnesses. An expansion of recent studies should lead to a better understanding of the causes of mental disorders, the relationship between environmental triggers and biological vulnerability, and the most effective means of treating the victims of mental illnesses. Development of effective treatments would improve not only the lives of victims, but also the economic productivity of the nation.

■ Brain and Spinal Cord Damage

Damage to the central nervous system is a major public health problem and the focus of significant research efforts on a number of conditions including head and spinal cord injury, epilepsy, infectious diseases that affect the brain and nervous system, stroke and genetic disorders. *Head and spinal cord injuries* kill or disable hundreds of thousands of U.S. citizens each year. Prevention of such injuries and the development and refinement of treatments are high research priorities. Steady progress is being made in finding new drug treatments for *epilepsy*, and new imaging techniques are helping scientists develop safe and successful surgical approaches for some patients. In the past decade, we have witnessed the emergence of four new *infectious diseases*—AIDS, Lyme disease, tropical spastic paraparesis and the spongiform encephalopathies—that seriously affect the brain and nervous system. This brings to nearly 40 the number of such diseases that afflict humans. In the United States *stroke* is the third leading cause of death and the most common cause of disability requiring rehabilitation. The social and financial costs of stroke are well over \$25 billion each year. Progress in stroke research and educating the public about research results have already reduced stroke deaths in the United States by 50 percent. This progress is likely to continue under Decade of the Brain initiatives. More than 1 million Americans have *genetic disorders* that affect the brain and nervous system. New molecular genetic techniques have helped scientists identify chromosomal locations for several genes associated with nervous system diseases, which may in turn open new doors to diagnosis and treatment.

Animal models for disorders of the brain and spinal cord are critically important for research on the mechanisms and possible treatments for these disorders. What scientists are learning from the use of monkeys in research has the potential to alleviate or cure neurological diseases such as Parkinson's and Alzheimer's. Preliminary research using cats paved the way to a new treatment that has substantially diminished the extent of paralysis following spinal cord injury. Animals will continue to be a valuable and necessary component of biomedical research during the Decade of the Brain.

■ Communication and Sensory Disorders

Because most disorders of human senses are invisible and not fatal, they have not received sufficient research attention. During the last decade tremendous advances have been made in understanding how cues in the environment are coded by the nervous system and what goes wrong in communication and sensory disorders. Great strides have also been made in developing methods of prevention and treatment. Priorities for the Decade of the Brain include clarifying the role of genetic and immunological factors in these disorders, developing new diagnostic techniques, and fostering new approaches to prostheses and other tools for augmentation or restoration of function. Interdisciplinary studies of sensory development, cognition and language development will improve the outlook for those suffering from a variety of sensory and communicative disorders.

■ Development of the Human Brain

The delicately balanced system that guides the assembly of the brain, especially during fetal development and in the months after birth, can sometimes fail, leading to often devastating disabilities. In the United States, we spend more than \$20 billion each year caring for children and adults with birth defects, growth failure, abnormal pubescence and other developmental disabilities. Understanding the mechanisms responsible for both normal and faulty development of the nervous system is essential for future prevention and treatment of these disorders.

■ Learning and Memory

The ability to learn and retain information may be the most important function of the nervous system. Research in this area is interdisciplinary, involving researchers in the neurosciences, cognitive psychology, behavioral sciences, engineering, and other technical fields of study. Fundamental brain research focused on learning and memory may yield important information for those concerned with treating individuals with learning disabilities, dyslexia, and other disorders related to learning and memory. There is also important economic potential in these studies. Our nation needs the technological productivity inherent in large-scale computer models and engineering devices that simulate intelligent behavior. Commercially viable, artificially intelligent computer systems are feasible in the Decade of the Brain.

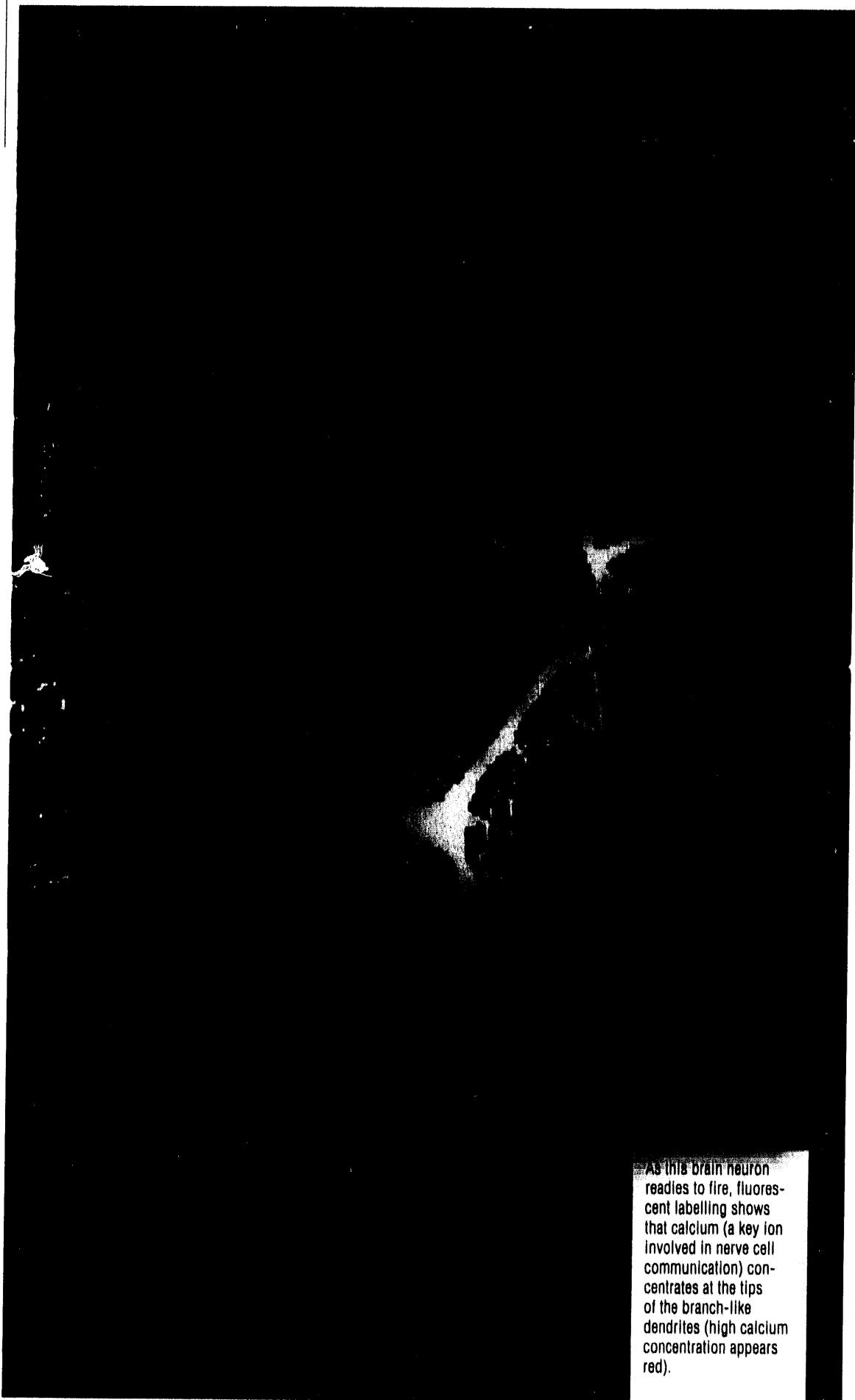
■ Rehabilitation and Restoration of Function

Successes in improving survival after injuries and illnesses involving the brain and nervous system have made rehabilitation and restoration of function increasingly important elements of medical care. The United States has achieved major accomplishments in rehabilitative techniques to help patients with a range of disabilities. The development of artificial limbs is especially notable, and pioneering accomplishments are emerging from research on neural prostheses—devices that directly assist the nervous system to replace or extend neurological function. These devices include auditory prostheses for the deaf, blad-

der control prostheses for spinal cord injury victims, neuromuscular stimulation for paralyzed individuals, and visual prostheses for the visually impaired.

■ Environmental Impacts on the Human Brain

Recent studies have improved our knowledge of how environmental factors, such as pesticides, dietary minerals and hazardous noise levels, cause nervous system dysfunction. Scientists are uncovering the basic mechanisms underlying neurotoxic events, and this new understanding has improved the ability to predict relationships between exposure and responses of the nervous system.



As this brain neuron readies to fire, fluorescent labelling shows that calcium (a key ion involved in nerve cell communication) concentrates at the tips of the branch-like dendrites (high calcium concentration appears red).

Cross-Cutting Program Areas

Basic Research

Basic neuroscience explores the brain and nervous system to discover the fundamental ways in which neurons work. The discoveries that come from this research are the building blocks needed to answer questions about the brain, behavior, disease and intelligence. Because the human brain is so complex and still largely difficult to study, it is necessary to carry out basic research on comparatively simpler biological systems and on ingenious models. For example, much of what is known about the basic mechanisms of the human retina came initially from work on the horseshoe crab. Basic studies on crayfish have given scientists a great deal of fundamental knowledge about spinal reflexes. And basic research on the squid giant axon has provided most of the fundamental knowledge regarding how individual axons conduct signals.

Basic neuroscience research in a broad range of fields is always needed to search for clues to brain function. Studies may be on systems ranging from a few neuronal cells in a laboratory dish, to invertebrate brains with only a few hundred cells, to brain subsystems in vertebrates. Vertebrate studies extend from ancient species such as the lamprey through levels of increasing biological complexity to the human. Complementing these studies are the basic laboratory experiments on the brain's function in behavior, on the way we use our senses to control movement, and on the interactions between endocrine and nervous systems.

One of the exciting aspects of current work on the brain is that disciplines that were previously insulated from each other, such as molecular biology, electrophysiology, neuroanatomy, psychology, engineering and computer modeling of neural networks, are coming together in ways that were only dreamed of just a few years ago.

Research on such disparate organisms as fruit flies and mammals is revealing fundamental similarities in the ways their nervous systems are put together during embryonic development. Scientists are isolating and characterizing genes on the molecular level that determine neural circuits involved in complex behaviors studied by psychologists. The findings at each level of analysis are considerably enriched, and in many cases made possible, by findings at other levels. Today an integrated approach to basic research on the nervous system is part of a natural progression building on past discoveries. Studies of the molecules involved in the development and function of brain cells interact closely with studies of animal behavior and human psychology.

Three technological developments in the past decade are driving current neuroscience efforts that are leading to novel findings. First, neuroscientists have new abilities to trace pathways and to identify particular cell types as the result of an explosion of new anatomical techniques, including powerful new stains and intracellular dyes for histology, voltage-sensitive dyes for real-time monitoring of whole populations of cells, immunocytochemical techniques to label classes of cells, brain-scan imaging (PET, MRI, etc.), and confocal microscopy for living tissue. Second, computers have come into virtually every lab, allowing real-time data analysis, sophisticated stimulus creation, very high temporal resolution of electrophysiological events, and tremendous data capture and storage capabilities. In a few cases, major computational efforts with supercomputers or parallel processors have led to development of theories about much more complex systems of model neurons. Third, the tools of molecular genetics are coming into neuroscience, with cDNA libraries, studies of protein expression, and genetic mutants and markers used in novel ways to probe normal and abnormal neural structure and function.

The impact of basic research is not always immediately evident. For example, the fruitful culmination of years of work in genetics now offers hope for treatment of neurogenetic disease. The discoveries that formed the foundation for scientific advancement in this research emanated from several fundamental discoveries dating back to 1928. In fact, the original work that clearly established the function of DNA took 13 years to complete. The benefits of this basic research are evident today in the biotechnology enterprises that develop new diagnostics, biologics, drugs, vaccines and gene therapy.

■ Accomplishments and Future Opportunities

The brain is the most complex organ of the human body. To understand how the brain functions, scientists study the cellular units of the brain called neurons. Today we know that neurons are enveloped by specialized membranes containing channels designed to regulate electrical excitability. The investigation of neuronal excitability has allowed scientists to begin to understand how neurons transmit signals. Stimulated by intracellular electrical activity, neurons communicate with each other by releasing chemical substances called neurotransmitters or neuromodulators. These substances act in a variety of ways to stimulate or inhibit other neurons. Thus, the brain is an intricate network of electrically and chemically active cells that are continuously influenced by the substances they contain, as well as by hormones and other agents carried in the blood.

More recent research has shown that neuronal communication is even more complex than originally expected. For instance, we now know that multiple "messenger" systems inside the neurons interact with the channels in the neuronal membranes, providing many sites where neural activity can be influenced.

Through very basic studies scientists actively seek to understand the function of the normal brain. This knowledge will provide insight into the mechanisms that underlie brain disorders and lead to the development of new treatments and preventions.

Most clinical advances in the brain and behavioral sciences are based on the findings of fundamental biomedical research. For example, a specific transmitter in the brain, dopamine, has been linked to a number of neurological disorders including drug addiction, schizophrenia, Parkinson's disease and Tourette's syndrome. Researchers now know that it is the dopamine-containing neurons that degenerate in Parkinson's disease. Therapies which block the breakdown of dopamine are being used to combat early stages of this disease. Similarly, schizophrenia is associated with enhanced activity of the dopamine system. Drugs that block the activity of excess transmitter are used for therapy.

Another major accomplishment over the past decade has been the development of a model to explain the euphoria induced by a variety of commonly abused drugs (e.g., cocaine, amphetamines, morphine, heroin, nicotine). Scientists think that many drugs are abused because they activate the dopamine system which, along with other neurotransmitters, mediates the experience of pleasure. Investigators use this model to develop potential treatments for drug addiction—cocaine antagonists are a particular focus—aimed at blocking drug-induced euphoria and craving.

Huntington's disease is a fatal, inherited neurological disease associated with the degeneration of motor systems. It directly affects 25,000 people annually. Specifically affected are cells that are involved in the coordination of movement, and cells which control perception and memory. Through basic research, scientists have linked selective cell destruction to a specific toxin that binds to a receptor on the neuron. Clinical studies will be undertaken to examine the effectiveness of receptor antagonists in slowing the progression of Huntington's disease. Major efforts should be made to discover new antagonists.

Basic research on movement has revealed that precise timing is essential for smooth and coordinated movement, and that postural adjustments are carefully controlled by mechanical impedance. Neuroscientists can analyze quantitatively how a single neuron matches the mechanical stress on a muscle in the maintenance of a movement or posture. Understanding this system will provide fundamental informa-



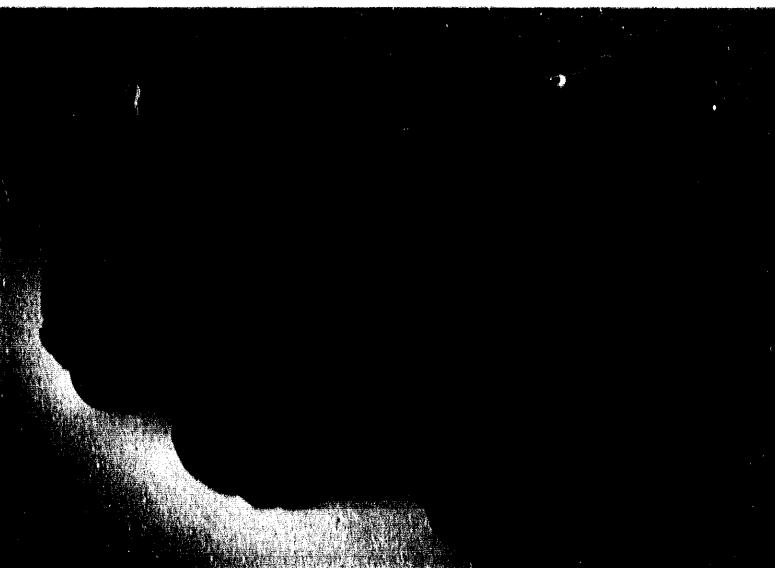
Basic research employs sophisticated tools to uncover the fundamental structure and workings of the brain and nerves. In this photo by National Science Foundation grantees, modern labelling techniques and high-power microscopy reveal a constellation of specialized brain neurons.

tion for numerous applications, ranging from the design of autonomous robots to the rehabilitation of stroke victims.

Modern research into the molecular basis of learning and memory is based on an understanding of some fundamental features of nerve cells. Scientists have achieved insights into how specific brain circuits may change as a function of experience (learning). For instance, investigators have discovered that in the hippocampus, an area of the brain that is associated with memory, a high-frequency electrical stimulation (analogous to experience) produces a long-lasting change (analogous to memory) in the response to that stimulation. Scientists have determined that this response is dependent on a specific neurotransmitter, and they are currently investigating the mechanism by which the response is developed.

Scientists investigating the neuroendocrine system have discovered a unique protein that appears to be essential to the biological clock that

determines daily rhythms controlled by the brain. This discovery, stemming from molecular biological studies of a gene in the fruit fly, has led investigators to the exciting finding that these same proteins are also present in the brains of vertebrates, indicating the importance of genes to brain function over millions of years in different species. Future experiments will clarify which cells are responsi-



The human brain—a 3-pound mass of interwoven nerve cells that controls our activity and thoughts—is at last yielding up its secrets. Neuroscience research has learned more about the brain in the last 10 years than throughout all of history.

ble for keeping the brain "on time." This research could have a significant impact on the productivity of shift workers, on the wakefulness of travelers required to cross multiple time zones, and on treatments for a variety of mental and physical disorders that require resetting biological clocks.

Food intake, appetite and body weight are controlled by the brain through interaction with peripheral signals. In recent animal experiments, investigators discovered that a peptide naturally found in the brain stimulates feeding when injected into a specific brain region, the hypothalamus. The hypothesis is that circulating glucose sugar raises the insulin level, which then acts to regulate the release of the peptide that stimulates appetite and feeding. Testing hypotheses such as this may ultimately lead to advances in understanding and treating appetite and body weight disorders.

Scientists studying sensory systems investigate how external physical stimuli are detected and translated by the brain. Scientists now understand that activity of the senses may be initiated by microscopic events between and within nerve cells. Research at this cellular and subcellular scale has been extremely active and fruitful.

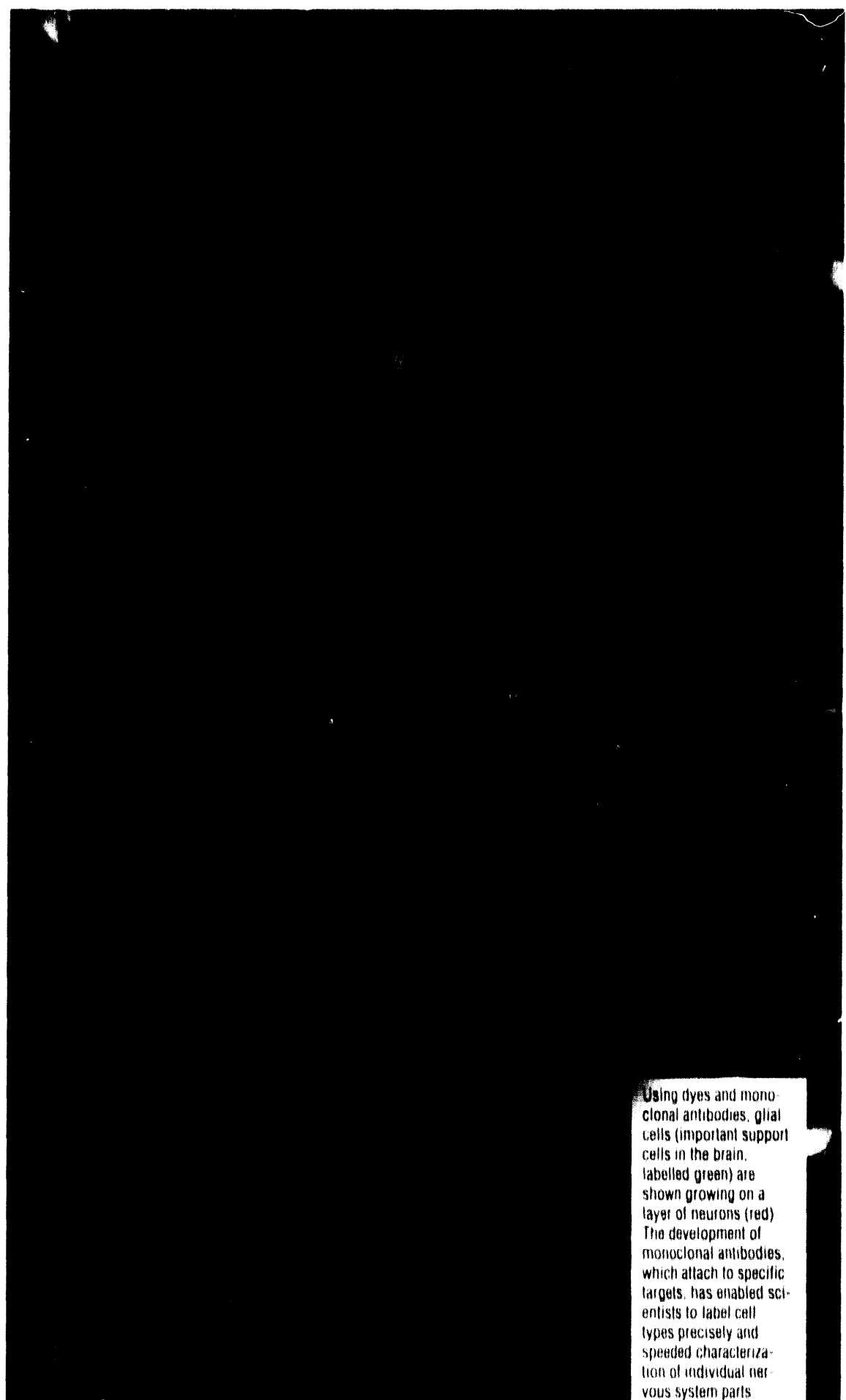
Modern techniques for monitoring the activity of neurons are enabling scientists to understand sensory perception in the complex centers of the brain, such as the primary sensory cortex. This work produces very precise quantitative data, often using human subjects. In primate vision, recent studies of motion detection have shown that the "local" process of detecting the movement of edges in a pattern can be separated from the "global" process of detecting the movement of a whole pattern. Scientists can identify separate areas of the brain where these processes occur. Similar studies of visual memory and recognition are bringing the investigation of cellular mechanisms to the study of higher cognitive functions.

A central question in the study of the brain and behavior is how the extremely complex nervous system is assembled, complete with just the correct number of cells and the right nerve connections and functional circuitry. Formation, growth, plasticity, regeneration and aging of the nervous system are all important phenomena related to this question. Studies of the embryonic lines of descent, or lineages, of individual neurons in simple systems are clarifying the importance of genetic and environmental interactions. Permanent dyes allow scientists to mark individual neurons and follow them throughout development of the organism.

Molecular neurobiology has thrived over the last decade. To date, investigators have localized the chromosomal site for more than 50 genes related to brain and behavioral disorders. To understand how genes cause disease and developmental disorders however, the genes themselves must be isolated and basic studies performed. The emergence of powerful new research technologies promises to assist greatly the study of identified genes by allowing specific mutations to be analyzed in laboratory animals. These techniques will also aid in revealing the neurogenetics of development, and hence the basis of nervous system malformations.

One example of research that yields basic information and new technologies that can be applied to understanding the brain and behavior—and maximizing human potential—is the newly initiated human genome research program. Sequencing the human genome will contribute to the discovery of genetic errors that underlie specific disorders, and thus one day permit the identification of individuals who are at risk for genetically based diseases of the brain. From this information, unique preventive and therapeutic strategies can be designed. The human genome program also includes the development of major new technologies in areas of automation, optimization and robotics, as well as in specific areas such as tunneling electron microscopy. These technologies will provide new bases for understanding the molecular function of the brain and new methods of diagnosis and therapy in many areas of medicine.

Future research will emphasize the origin of congenital abnormalities, focusing on the initial formation of the neural tube, which develops into the brain and spinal cord, and the generation of neurons and their supporting cells. The fate of individual cells and their progeny will be defined and the plasticity of the nervous system will be assessed. Investigators will be able to identify the genes that direct the development of the brain and the maintenance of individual cell function in



Using dyes and monoclonal antibodies, glial cells (important support cells in the brain, labelled green) are shown growing on a layer of neurons (red). The development of monoclonal antibodies, which attach to specific targets, has enabled scientists to label cell types precisely and speeded characterization of individual nervous system parts.

animal models, and then compare these data with information on mapping and sequencing obtained from human genome studies.

An example of this research is that conducted on retinoblastoma, a cancer of neural tissue in the retina that affects about 500 American children each year. Unchecked, retinoblastoma spreads to the optic nerve and other parts of the eye. Most retinoblastoma is passed along through a defect of a chromosome on which part or all of the retinoblastoma gene is missing. Research has led to the discovery of the gene, which, when present and functioning properly, codes for the protein that controls cancer growth in the inherited form of this disease. More recently, researchers have shown that introduction of normal retinoblastoma genes into tumor cells causes them to behave like normal cells, thereby opening new avenues for a potential therapy for this cancer. Other researchers have developed a mouse model that will allow the study of malignant transformation of neural tissue, and will aid those attempting to develop and test drugs for retinoblastoma therapy.

Phenylketonuria (PKU) is an autosomal recessive disorder with an incidence of about 1 in 14,000 births in the United States. Affected individuals lack a liver enzyme, phenylalanine hydroxylase (PAH). Untreated, PKU is characterized by severe mental retardation, behavioral problems, epilepsy and other signs of neurologic impairment. Screening programs for PKU in newborns have been successful in diagnosing infants, and early dietary therapy has largely prevented the development of impairments. Using recombinant DNA technology, the normal human gene responsible for the production of the PAH enzyme has been produced and cloned. The development of an animal model that is genetically deficient in producing PAH is important to determine whether insertion of the gene could supply the critical enzyme activity and to contrast the effectiveness of gene therapy with dietary therapy.

Thus, as Louis Pasteur once said, "Chance favors the prepared mind." Basic researchers are seeking to prepare minds and to provide the knowledge necessary to make and use important discoveries. To continue to achieve clinical successes, we must maintain our focus on the basic research that leads to clinical, educational, behavioral and technological applications. It is only through a strong science foundation that we will realize the potential of the Decade of the Brain.

Technology

For the past 50 years the major force motivating basic research in the brain sciences has been, and continues to be, the belief that through such research scientists will be able to effectively diagnose and treat injuries to, or diseases of, the nervous system. Thus, clinical application of basic research on the nervous system has been the dominant "driver" for much of the research, both past and present. There is a new "driver" now emerging to provide additional motivation for the strong support of basic research in the brain sciences. This driver, or

application area, is technological leadership and economic vitality. Recent advances in our understanding of the nervous system are stimulating the development of new high technologies in the design of advanced silicon chips as well as revolutionary computer architectures. A major emphasis on basic brain sciences during the Decade of the Brain will undoubtedly accelerate these and other efforts.

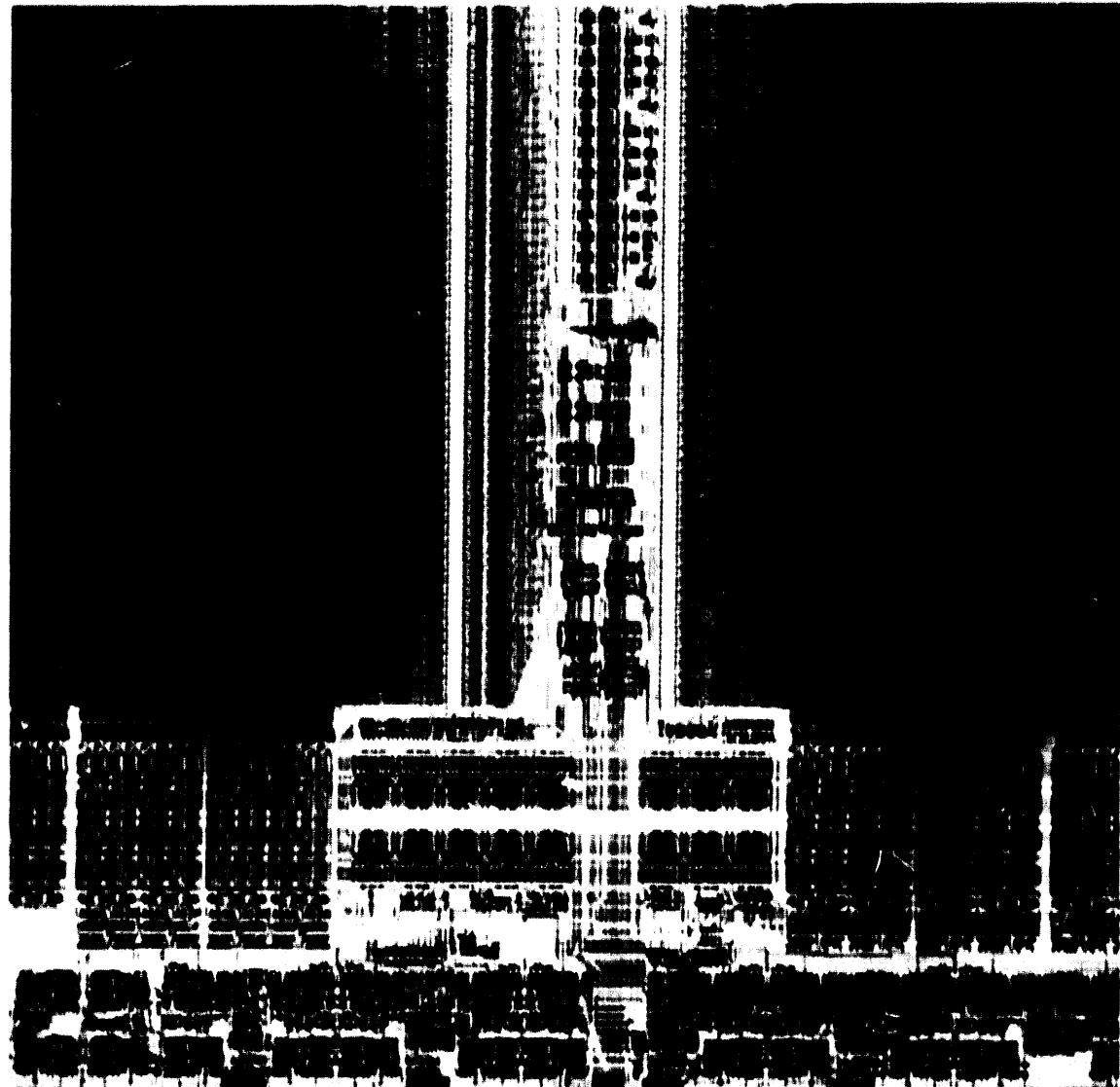
■ Accomplishments

Three technological developments in the past decade are now providing new opportunities for brain research. First came an explosion of new techniques for understanding the brain, including new brain imaging technologies. These imaging technologies are providing clinicians and researchers alike with the capability to understand brain function and dysfunction in ways never before possible. Second, new, sophisticated computers and associated modeling techniques have been developed, providing scientists with tremendous capabilities for capturing, storing and analyzing data, and creating biologically plausible simulations of brain functions. These computers and techniques are now leading to the development of new theories about complex systems of artificial networks of neurons that are stimulating the development of new computer designs likely to revolutionize the U.S. computer and solid state silicon chip industries. Third, the tools of molecular genetics are being applied to brain research. Gene libraries, studies of the proteins produced as a result of genetic direction, and genetic mutants and markers are also being used in novel ways to probe normal and abnormal neural structure and function. The resulting new knowledge will lead to the ability to detect and correct many genetically based diseases of the brain and central nervous system—diseases that are currently untreatable.

Imaging Technology. The non-invasive nature of new brain imaging techniques allows investigators to observe directly deep brain structures and their functional activities. Chief among these techniques are positron emission tomography (PET), magnetic resonance imaging (MRI) and magnetoencephalography (MEG).

With PET, investigators have achieved significant advances in understanding the normal and the diseased brain. PET can measure non-invasively the relative levels of metabolic activity in the human brain and can image the working parts of the brain—a feat barely imagined 20 years ago. PET is being used to study a large number of disorders, including stroke, schizophrenia, brain tumors, epilepsy, depression, Parkinson's disease, Alzheimer's disease, Huntington's disease and Tourette's syndrome. The technique is useful in finding clues to other medical problems such as drug addiction, and in evaluating the effectiveness of medications. For example, PET studies show a correlation between the distribution kinetics of labelled cocaine in the brain and the subjective "high" associated with the abuse of this substance. This may lead to insights into the mechanisms of addictions and to potential therapies. Investigators are also using PET to study higher cognitive functions such as learning, thinking and memory.

MRI, another brain imaging technique, uses magnetic fields and radio waves to produce an image that provides information about the structure and biochemistry of the brain. MRI scans complement PET scan



This silicon chip, designed by a Department of Defense contractor and modeled on human nerve networks, has the processing capability of 1000 brain neurons.

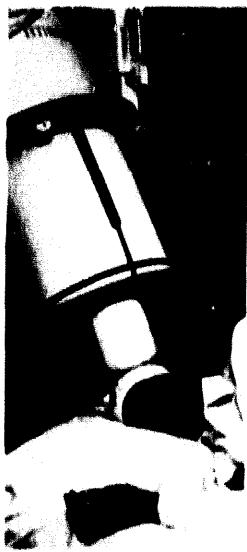
data by providing detailed anatomical images of both surface and deep brain structures. Because of MRI's ability to see through bone, it has been especially useful for scanning the brain and spinal cord in areas which have previously remained hidden. Through spectroscopy, the MRI can also be used to examine the chemistry of living tissues, detecting changes caused by disease.

MEG is the newest technique being used for diagnostic purposes. The small electrical currents produced by nerve cells create magnetic fields, which can be measured outside the brain by a magnetometer. Recording these measurements has several advantages over previously used techniques: the magnetic fields emerge undistorted through the skull and scalp, no electrodes are needed, and the scan can be made without physical contact. Extraordinary three-dimensional localizations of brain lesions are being made possible by this new physiologic technique.

Neural Networks and Neurocomputing. In the past two decades the amount of information known about nervous systems has expanded explosively. At the same time, scientists have made dramatic advances in silicon chip technology and conventional computer science. These concurrent events, coupled with the growing awareness of the limits of conventional computing, have set the stage for what is likely to be a scientific revolution having dramatic and widespread influences throughout science, technology and, accordingly, society. Neural networks and neurocomputing represent radical departures from conventional approaches to digital computers. Neurally inspired and biologically realistic computer processing elements have already been shown to have the capacity to do useful, complex computations, outperforming, in some cases, similar computations made by conventional computers.

Current research programs are directed towards an understanding of neural information processing based upon brain circuitries. Neural systems are being evaluated for their capacity to perform computations required for image processing, acoustic analyses, speech recognition, signal classification and the organization of motor output. Memories based upon neural network concepts are investigated to assess their properties and information-storage capacity. Neurophysiological and neuroanatomical data are used to understand the major classes of distinct biological neural networks and how they differ. The goal is to better understand the processes used by the brain in its role as a biological information-processing system and to clarify the nature of neural computations in network processing. Significant progress in this research will produce a new generation of biologically inspired artificial neural networks and computers, while at the same time providing major insights into the nature of biological information processing, human learning and memory, and the fundamental organizational principles of the brain.

This research program is explicitly interdisciplinary in nature and in content, with research teams composed of neuroscientists and engineers, physicists, mathematicians and computer scientists. Progress to date has been significant. If pursued aggressively, this unique and exciting scientific and technological adventure will reinvigorate the United States chip manufacturing and computer industries and



This patient is undergoing MEG, the newest technique for imaging and diagnosing brain disorders. MEG detects magnetic signals created by the small electrical discharges of nerve cells.

could help the United States strengthen its position as a leading technological force in information processing.

Molecular Genetics and Biotechnology. About one-third of the functional human genome is involved in brain activity, and at least 500 inherited diseases have major neurological manifestations. As a whole, these disorders occur in more than 1 million people in the United States. Particularly devastating are children's disorders such as Tay-Sachs disease, the leukodystrophies and Batten's disease, all of which inevitably lead to progressive brain deterioration, dementia and death.

Within the last decade, the use of molecular genetic techniques has allowed the identification and location of several genes that are associated with diseases of the nervous system. These studies have already led to presymptomatic and carrier detection in many disorders and to the identification of the disease-causing gene in others. The cloning of these genes will lead to more accurate testing and to the development of model systems in which to examine novel treatments. (See *Basic Research*.)

Although in the past genetic linkage studies were limited by the lack of markers to scan the human genome, rapid advances have increased the number of candidate genes and markers so that much more specific areas of the genome are being mapped. Using molecular genetic techniques—coupled with supercomputer, computational and model-building capabilities—abnormal genetic sequences can be detected and traced to specific genes. The national effort to map and sequence the human genome further increases the likelihood that defective genes can be identified and their expression better understood.

There have been several recent success stories in neurogenetic research. One is the discovery of the gene responsible for Duchenne muscular dystrophy. Using the tools of molecular biology, scientists found the gene and its product, dystrophin, which is needed for normal muscle function. This discovery led to a treatment in which normal muscle cells are injected into defective muscle, become fused with the host cells and produce dystrophin, the missing protein product. The gene for neurofibromatosis I also has been discovered recently, as has a gene which codes for the protein that controls cancer growth in the inherited form of retinoblastoma, a cancer of neural eye tissue. Researchers have also localized a gene for retinitis pigmentosa, an array of diseases that affect vision, to chromosome 3, which also car-

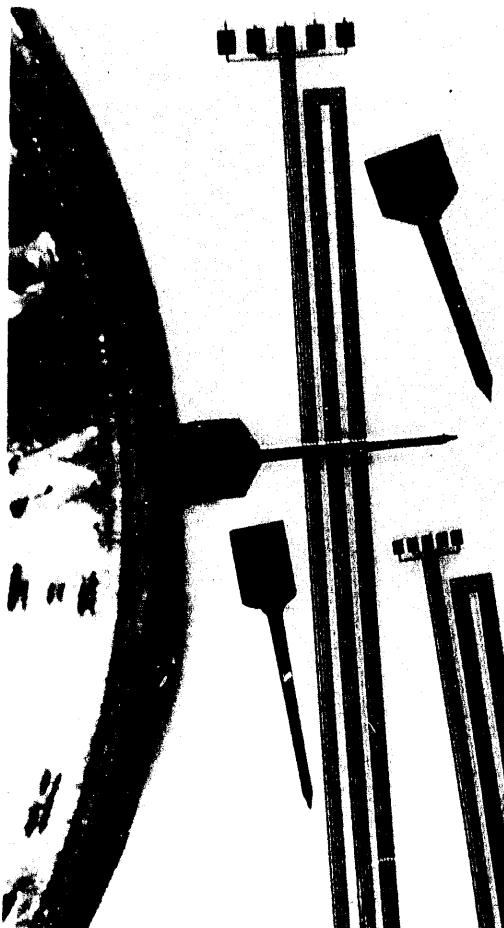


Researchers sponsored by the Department of Energy are devising and testing new brain imaging technologies. Here CT and MRI studies of a 15 month infant with intractable seizures showed no abnormal brain structures. Experimental PET, however, revealed metabolic defects throughout the left hemisphere which were subsequently treated surgically. Since treatment, all seizures have stopped and the child has developed normally.

ries the gene for rhodopsin, the light-sensitive protein found in photoreceptors.

Following preliminary reports of linkages in bipolar (manic-depressive) disorder, schizophrenia and Alzheimer's disease, investigators are increasingly applying molecular genetic methodologies and biotechnology to the study of behavioral and psychiatric disorders. Research over the last two decades in developmental neurobiology and genetics

Scientists creating neural prostheses to aid disabled individuals are developing tiny probes and cables—shown here adjacent to a coin—able to interface with nerve cells.



for certain behavioral disorders such as autism is also paving the way for understanding the molecular and neurobiological basis of childhood behavioral disorders.

Techniques are now being explored to implant genetically altered cells into the nervous system or to genetically alter cells within the nervous system itself. In addition, recent success in the treatment of Gaucher's disease using enzyme replacement therapy establishes a template for similar therapy of other genetic metabolic disorders. Such studies are very exciting and may lead to treatments of Parkinson's disease and Huntington's disease and to methods of modulating neural pathways. These studies will also provide basic insights into the development of the nervous system, the repair of the nervous system after stroke or injury, and the mechanisms of memory, pain and seizures.

■ Future Plans and Potential Benefits

With the development of new brain imaging technologies that allow direct observation of the active brain, scientists will soon be able to determine how structure and function correlate in the normal and diseased human brain. The mapping of some areas, such as vision, is moving forward quickly, while the understanding of more complex processes such as memory or cognition remains a long-term goal. With MEG, for example, it likely will be possible to monitor the activity of the active brain and to track its changes in both time and space. This will permit the noninvasive localization of the discharging lesions that are the source of epileptic seizures, allowing for accurate surgical removal and obviating the need for invasive techniques of diagnosis such as the currently used depth electrode recording from the brain. Through a combination of the imaging techniques now available, and

the utilization of sophisticated computer programs to manipulate the images and data received, a functional map of the human brain is an attainable goal by the end of the Decade of the Brain.

Research on neural circuitry has significant potential for application in the following areas: the design of novel computers based on biological processes, more efficient uses of massive parallel processing systems for high-speed computers and the production of artificial intelligence sys-



This computer model of a specialized brain neuron depicts the fine-tuned distribution of electrochemical potential along the nerve cell's trunk and branches. Such computer modeling provides insight into how neurons store information.

tems with enhanced "cognitive" capabilities. This emergent technology, based upon biologically inspired information processing strategies, will result in major changes in the computer industry of the future. This technology can provide the United States with an opportunity to regain its preeminence in the highly competitive and economically important international struggle for leadership in the world's information-processing technologies.

What is it that neural networks should compute? What aspects of biological intelligence would scientists like to emulate in a new generation of computational devices? The answers to these questions are central driving forces that are pushing basic research into an arena filled with applications and technological opportunities. Optimally, neural networks should learn spontaneously as a result of experience, seek optimal solutions for a given problem, accurately process ambiguous data that is only approximately matched to what has already been stored in memory, perform hypothesis testing and probability estimation, and adjust rules used in processing information when presented with new input data.

Achieving these capabilities will require coupling new information derived from biological nervous systems with advances in technology, computer design, optical information processing, algorithm development and adaptive signal processing. Central to the enterprise, certainly in the long view, will be the identification of relevant principles and abilities of biological nervous systems to be emulated in artificial neural systems. It is not, and probably should not be, a goal of the neural network research enterprise to duplicate a living human nervous system in all of its mystery and complexity. Rather, new insights into principles of biological computation will emerge and should help us develop new approaches to the use of computers.

Over the next decade the genetic sequencing programs started in the 1980s will be enhanced by the ability to integrate their results with the mapping and sequencing information obtained from additional human genome studies, as well as by further technological advances in molecular biology and microscopy. These and other developments will provide us with powerful tools for the identification of the genes that are associated with both normal and abnormal formation of the brain and nervous system. These efforts have great potential for uncovering the knowledge base necessary for understanding the source of malformations and disease processes in the human nervous system.

The search for genetic determinants of growth, development and regeneration of nervous tissue also should provide new potential approaches to therapy of brain and behavioral disorders. Other areas for future research include: 1) isolation of the genes for the many devastating disorders of the brain and nervous system, including Batten's disease, schizophrenia, Huntington's disease, tuberous sclerosis, Alzheimer's disease, dystonias, retinal diseases, Down syndrome, alcoholism and the tendency to seek drugs; 2) studies on the biochemical characterization of neurogenetic disorders, and investigation of the structure, function, expression and control of disease genes and other genes relevant to neuronal development; and 3) development and evaluation of treatment, including studies on gene therapy, genetically altered cell line production, bone marrow transplants, chemical carriers and other targeted delivery systems to the brain.

International Activities

Disorders of the brain and behavior cross all geographic boundaries, directly or indirectly affecting everyone in the world. Chinese men and women suffer brain damage from sudden stroke; French newborns suffer epileptic seizures; an elderly Canadian woman loses control of her body and mind to Alzheimer's disease; young adults around the world grow increasingly confused, their memories eroded by the neurological complications of acquired immunodeficiency syndrome (AIDS). The economic and social costs of these disorders are borne by all.

The causes of brain disease are equally diverse: flawed genes, viruses, trauma, blood clots or a defective immune system. Sometimes, a disorder's cause eludes scientists, and little more is known about a disease than its name. Yet the vast geographic range of brain and behavioral disorders presents scientists with an ability to gather and compare a large pool of data. For instance, investigators seeking factors that predispose some people to stroke can compare different populations around the world to help elucidate the roles played by genetics and environment. Similarly, research on epilepsy benefits from incidence differences in North and South American countries.

A dramatic example of the potential for the international application of research is the fact that effective application of current knowledge—

including information on the significance of vitamin A—could prevent up to 80 percent of all blindness around the world. Current global efforts are designed to heighten public and governmental awareness of the problem of blindness, mobilize available resources, promote the development of new programs where needed, and increase the effectiveness of existing programs. The United States currently supports international research on blinding diseases that have a major worldwide impact.

In some cases, international research allows scientists to seek out and study extended families affected by brain diseases linked to a genetic cause. Such families are rare and offer valuable clues about the causes, complications and treatment of neurogenetic disorders. Hence, U.S. scientists are turning to Europe and Canada to extend knowledge about familial Alzheimer's disease and to Israel for insights into a rare metabolic disorder, Niemann-Pick disease.

■ Accomplishments and Future Opportunities

To pursue all possible leads about the brain in health and disease, the United States supports and works with scientists in institutions throughout the world. International programs take many forms:

- joint research conducted under country-to-country agreements,
- efforts involving multinational organizations,
- research grants and training programs,
- collaborative research projects uniting individual U.S. scientists and foreign colleagues, and
- international meetings to share knowledge.

Aging. Reported differences in the occurrences of Alzheimer's disease and multi-infarct dementia between Asian (Japanese as well as Chinese) populations and European-ancestry populations have stimulated further study of these trends. Investigators in Seattle, Japan and Taiwan plan to conduct parallel studies in Asian-ancestry populations using similar methodologies to ensure that research results will be comparable. Using the Swedish Twin Registry, a U.S. scientist and a collaborator in Sweden are developing a study of the genetics of Alzheimer's disease.

Studies of a rare, fatal dementia, Creutzfeldt-Jakob disease (CJD), have identified a mutation affecting the gene for amyloid precursor protein in all Slovakian and Israeli patients studied. Amyloid precursor protein is of particular interest to scientists because it is converted to an abnormal form in the brains of CJD patients. This deformed protein also can accumulate in abnormal deposits, called amyloid plaques, in patients' brains. Such plaques are also a hallmark of Alzheimer's disease, a better known and more common form of dementia. While different proteins create the amyloid deposits in Alzheimer's and CJD, information about how the plaques are formed in CJD may lead to new understanding of the mechanisms of both diseases.

American scientists working to uncover the cause of Alzheimer's disease are collaborating with an international team of investigators from



the Soviet Union, United Kingdom, Federal Republic of Germany, France, Mexico, Italy, Belgium and Canada. Through genetic studies of more than 40 families with a history of Alzheimer's disease, these scientists have uncovered new evidence that Alzheimer's may represent more than one disease, resulting from various causes. This team expanded earlier results showing that some cases of inherited Alzheimer's disease are linked to specific genetic defects on chromosome 21. In their recent research, they found that most patients who developed familial Alzheimer's disease early (before the age of 65) had a chromosome 21 defect. In contrast, most family members who developed Alzheimer's disease after age 65 did not have this genetic defect.

Behavioral and Mental Disorders. Behavioral and mental disorders are the targets of collaborative research in many regions of the world. For example, scientists from the United States are working with the European Science Foundation to study the molecular biology of mental illness. U.S.-Indian collaborations are addressing the problems of schizophrenia, affective disorders and childhood mental illnesses.

Brain and Spinal Cord Injury. Canadian scientists are focusing on a broad range of topics relevant to injury and malignancies of the nervous system. They have developed a model of the blood-brain barrier using cultured human cells and are employing this model to test drugs and other substances for their ability to enter the brain. Investigators are leading a 5-year multicenter trial of the usefulness of carotid endarterectomy in preventing stroke. This commonly performed surgery clears fatty deposits from major arteries supplying blood to the brain, but its usefulness is not clearly established. Other investigators are testing the neuroprotective effects of calcium-blocking agents. These agents, which are currently used to lower blood pressure, may help limit the death of brain cells after stroke. Important work on the causes and treatment of stroke is also proceeding in the People's Republic of China, the Federal Republic of Germany, Sweden and Italy.

Communication and Sensory Disorders. Cataract is the most widespread form of curable blindness and will become even more significant as the world population ages. In conjunction with the Pan-American Association of Ophthalmology and Helen Keller International, the United States has continued to help establish Cataract-Free Zones in several Latin-American countries. The techniques developed in all of these projects will have important implications for reducing the total cost of routine cataract surgery.

Particularly in Asia, vitamin A deficiency is a public health problem and the leading cause of blindness among preschool-aged children. The most effective way of providing affordable prevention programs is under study by U.S. scientists and Nepal's National Society for the Prevention and Control of Blindness.

Participants in the U.S.-U.S.S.R. Program for Health Cooperation in Eye Diseases have reaffirmed the need for continued collaboration under the program, which was begun in 1987. During the past year, scientists continued to pursue these collaborative studies, which include epidemiologic research and investigations of glaucoma,

cataract and immune function of the eye. Under a Medical Science and Public Health Cooperative Agreement, scientists from both countries have conducted joint research on the biological effects of low-frequency electromagnetic radiation. Scientists conducted collaborative experiments to evaluate sensitive tests that measure the biological effects of electromagnetic fields on the nervous system and to validate research results obtained in the United States and the Soviet Union.

The United States and the Indian Council of Medical Research have developed a collaborative blindness research program that includes projects to reduce blindness in India from vitamin A deficiency, cataract and Fales' disease. The United States is also joining collaborative research to improve India's mass cataract surgery intervention program.

The United States has a number of cooperative research programs with various foreign partners (the Soviet Union, the Federal Republic of Germany, France,

Canada and the European Space Agency) aimed at using weightlessness to study neurovestibular physiology. Space flight provides a unique environment for scientists to study the basic physiological processes by which the nervous system senses acceleration and regulates perception, orientation and body position. This international research focuses on otolith function, the vestibular-ocular reflex, optokinetic responses and visual-vestibular interactions.

Development. Israel-U.S. Binational Science Foundation grants are assisting investigators from a U.S. laboratory in two scientific undertakings. An analysis of how nerve cells communicate in the developing spinal cord unites U.S. scientists with investigators from Jerusalem. In particular, this team is trying to understand the relation of synaptic connections and the properties of nerve cells to the development of coordinated movements. Theoretical studies of the ways in which neurons process electrical signals during movement are also being conducted.

A team of U.S. scientists has been cooperating with Yugoslavian colleagues on a study of the ability of EEG to predict recurrent febrile seizures in children.

Adequate nutrition is critical to normal development and performance. Efforts to identify and provide optimal nutritional intake are the focus of international research and assistance programs.

Drugs and the Brain/Addiction. An agreement between the United States and the National Institute of Mental Health and Neuro Sciences



The weightlessness of space provides a unique opportunity for scientists at the National Aeronautics and Space Administration to study the physiology of body systems that sense gravity and motion and control posture and movement.

in Bangalore, India, has provided a framework for exchanges on current research in substance addiction. This scientific exchange is supported by a variety of diplomatic efforts to foster international cooperation to prevent and reduce the demand for illicit drugs.

Environmental Impacts. Health effects of the environment truly know no international boundaries. Collaborations between U.S. scientists and their international counterparts include studies in Taiwan on the

effects of human exposure to polychlorinated biphenyls resulting from the accidental contamination of cooking oil. Children born to mothers who had consumed the tainted oil showed abnormalities on behavioral assessments and delay of developmental milestones.



After 3 months in a targeted feeding program this Bangladeshi infant has gained weight and strength offering the hope of a healthy future. The Agency for International Development promotes programs directed at restoring physical functions and reducing the potential for brain deficits. (Photo courtesy of Irwin J. Short, Concern Worldwide.)

research, especially in societies moving toward a more industrialized economy with the accompanying need for more skilled labor. Also driving this research area are advances in molecular biology and brain imaging that allow new insights into how the brain acquires, stores, retrieves and uses information.

Rehabilitation and Restoration of Function. Scientists from a U.S. laboratory and the John Curtin School of Medical Research in Canberra, Australia, have been studying nerve-cell arrangements in brain regions that control complex voluntary movements. The scientists are looking at how different colonies of neurons transmit messages along the spinal cord to activate or inhibit specific muscles or closely related groups of muscles. The investigators are particularly interested in the function of a brain area called the "supplementary motor area," which plays a mysterious role in initiating and guiding movements. Understanding the role of various regions of the brain and spinal cord is vital to improving rehabilitation and therapy programs for patients with brain and spinal cord injury.

A long-term study of calculation disorders in brain-damaged patients unites scientists from the United States with French investigators in Paris. The international team is testing brain-damaged patients to define the mental steps required to process numbers and calculate. They will then map where these steps take place in the brain.

Activities With International Organizations. Several U.S. Federal agencies are members of the World Health Organization (WHO), and support its Collaborating Centers in the Neurosciences. Scientists at these Centers, which are strategically positioned around the world, investigate brain and behavioral disorders and develop community programs. Among the disorders studied are stroke, epilepsy and disorders related to childhood nutritional and developmental problems. Centers

exchange scientific information by sponsoring conferences and courses and publishing proceedings of those events. These programs also involve efforts to increase the ranks of qualified neuroscientists willing to undertake sophisticated investigations in more isolated, less developed regions. The International Neurosciences Fellowship Program brings investigators from developing countries to the United States for advanced research training. They then return home to become leaders in neuroscience research and education in their own countries.

U.S. Federal agencies spearheading Decade of the Brain efforts will promote international collaboration with scientific agencies and organizations in the following countries, all of which have begun or are planning Decade of the Brain activities:

Mexico	Czech and Slovak Federal Republic	Hungary
Venezuela	Canada	Italy
Ecuador	Federal Republic of Germany	Spain
The Netherlands		



Like microscopic phone cables, axons (seen here as long, thin strands) are elongated nerve cell components able to carry messages swiftly across relatively large distances

Drugs and the Brain/Addiction

Drug abuse, which includes alcohol abuse and alcoholism, is a major health problem that affects almost every family in our country. Illicit drug use is not confined to a discrete segment of the population. The problems created by drug abuse, such as premature death, lost human potential, increased health care costs, crime and lost productivity, affect everyone. Nearly 1.6 million American teenagers are currently using illicit drugs, and surveys of women of child-bearing age reveal that 8 percent have used illicit drugs in the previous month. Furthermore, in a 1989 survey of 21 major U.S. cities, illicit drug abuse was implicated in 139,685 emergency room visits and in 7,162 emergency room deaths. The impact of alcohol abuse and alcoholism is equally devastating. Fifty percent of all traffic fatalities, 93 percent of all drowning deaths (the third leading cause of injury-related death), and 3 percent of the total deaths in the United States are alcohol related.

The common denominator of all addictive substances, including alcohol and nicotine, is their profound, deeply ingrained effect on the brain. This effect may begin even before birth. The use of any drug during pregnancy poses a risk to the developing fetus. Alcohol in particular has been shown to have the capacity to produce profound damage to the fetal brain. Tragically, the alcohol-induced fetal alcohol syndrome is one of the leading known causes of mental retardation. After birth, drugs may interfere with learning and memory. In addition, cocaine, particularly in the form of "crack," appears to have caused a dramatic increase in stroke in young adults; other young cocaine users may suffer complications such as seizures, brain hemorrhage and psychosis.

The monetary cost of drug and alcohol abuse is also staggering. Health care costs for treatment alone are approximately \$2.7 billion a year for illicit drug abuse and \$8.7 billion a year for alcohol abuse. When lost wages, crime and other consequences are considered, the total cost of drug and alcohol

Research funded by the National Institute on Alcohol Abuse and Alcoholism shows that patterns of brain electrical activity — shown here as color shading — differ in normal individuals (top) compared to those in people at high risk for developing alcoholism (bottom).



abuse approaches \$150 billion a year, making it one of society's costliest health problems.

Drug addiction and alcoholism are diseases of the brain, resulting from repeated self-administration of these substances. This exposure to drugs and alcohol results in fundamental, albeit incompletely understood, changes in the structure and function of the brain. These changes are manifested in a variety of functional changes, including intense craving and drug-seeking behavior, an inability to experience pleasure, physical dependence on and tolerance to the drug, withdrawal effects, depression, paranoia and psychosis.

Alcohol, nicotine and drug dependence result from a complex interaction of biological, genetic and environmental factors. Drug- and alcohol-dependent persons experience intense craving, tolerance and severe physical effects from withdrawal, all of which may contribute to uncontrollable use. Many questions regarding the causes and treatment of the addictions remain unanswered, but progress has been made toward both a genetic and biochemical understanding of addiction. Additionally, researchers are beginning to define the characteristics of effective treatments for those patients with chronic addictive disorders who tend to relapse. It is hoped that research conducted during the Decade of the Brain will result in major breakthroughs in our understanding of addictive disorders and in the subsequent development of more effective treatment and prevention technologies.

■ Accomplishments

One of the most important advances in understanding drug addiction has been the identification of the precise molecular sites, or receptors, in the brain where drugs exert their action. The discovery of opiate receptors and naturally occurring opiate peptides in the brain started a revolution in our understanding of the role of peptides and multiple receptors in brain function. Recent studies have also identified the brain receptors for tetrahydrocannabinol (the active chemical in marijuana), phenylcyclidine (or PCP) and cocaine. The basic genetic mechanisms regulating receptor function are being studied and elaborated.

This PET scan of normal and cocaine-treated brains by scientists at the National Institute on Drug Abuse demonstrates that cocaine use decreases metabolic activity. Warmer colors (red and yellow) correspond to areas where the brain is using high levels of energy in the form of glucose. Cooler colors (blue and violet) mark areas of lowest glucose utilization.



Efforts to understand the neurobiological mechanisms of drug addiction have also facilitated substantial progress in disorders other than drug abuse. For example, the medication naltrexone, an opiate antagonist that was developed to treat heroin addiction, may also be useful for treating a wide variety of other medical conditions, including sudden infant death syndrome. In addition, discoveries related to endogenous opioids may have far-reaching implications outside the realm of drug addiction, and could be important for treating stroke, neuropsychiatric disorders, chronic pain, complications related to paraplegia and other disorders.

Another major accomplishment has been the development of an animal model for drug abuse. This is one of the most effective models ever developed for research on a human disease. Some animals will voluntarily self-administer the same drugs of abuse that humans do, while ignoring most drugs which are not abused by humans. These animals exhibit the same compulsive drug-seeking behavior seen in people addicted to drugs and will self-administer pleasure-stimulating drugs repeatedly, to the point of ignoring other rewarding stimuli such as food or the companionship of other animals.

Using this animal model in conjunction with a variety of neuroscientific technologies, scientists have found evidence of specific brain systems that activate "reward centers" in response to the environment. In these reward centers, intense sensations of pleasure are believed to be generated in response to natural stimuli, such as food and sex, and to artificial stimuli, such as drugs. A drug's ability to stimulate the reward centers appears to be the reason why people addicted to drugs are obsessed with obtaining and using drugs.

This brain-reward model helps to explain the uncontrollable nature and intensity of drug dependence and provides researchers with a tool to study pharmacological and behavioral factors that control drug-seeking behavior. The model is now being used to understand how brain-reward centers function naturally and how drugs influence these brain systems, and for the development of potential treatments for drug addiction.

Related studies have shown that the brain systems responsible for drug-seeking behavior are anatomically distinct from those mediating physical dependence on drugs. Animals will compulsively self-administer morphine directly into the reward centers of the brain, but are not physically dependent on morphine, i.e., they do not go into withdrawal when morphine is not available. On the other hand, animals do not self-administer morphine into another specific area in the brain but become physically dependent on the drug following passive infusion into this site.

During the Decade of the Brain, scientists will also continue in their efforts to understand and treat nicotine addiction. Our understanding of this addiction has been advanced by the identification of nicotine receptors and the genes coding for subunits of these receptors. Future studies will assess the role of such genes in nicotine tolerance and dependence. In addition, PET scanning will help identify the biological substrates of behavior supporting human nicotine dependence.

Significant advances have also been made in understanding the link between the abuse of drugs or alcohol and a genetic predisposition or vulnerability toward seeking drugs or alcohol. Studies of families, twins and adopted children, as well as animal models, have established a familial predisposition for alcoholism. In addition, recent studies of animal models have suggested that there may be a genetically determined predisposition toward the abuse of opiates and psychomotor stimulants such as cocaine. Molecular biologists are currently working to better understand the genetics of vulnerability to drug abuse by developing transgenic mice which carry the human gene thought to be a factor in the vulnerability to certain kinds of drug abuse. These mice are valuable because they provide scientists with a tool that may lead to a clearer understanding of the role of genetics in drug abuse behavior, which in turn will facilitate the development of effective treatments.

■ Future Plans and Potential Benefits

There are several areas in which significant advances are expected during the Decade of the Brain. These include: understanding the specific biological effects of drugs on the structure and function of the nervous system; development of treatments for intervening in the various stages of drug use, such as craving, euphoria, withdrawal and relapse; clarifying the adverse effects of drugs of abuse on development and brain functioning; and defining the influence of genetics on drug-seeking behavior and addiction.

In order to develop the most effective treatments for drug abuse, it is necessary to have a clear understanding of how drugs interact with the brain. To accomplish this, scientists will continue in their efforts to understand the basic neurobiology of how drugs affect nerve cells and brain functioning. They will work to expand the model of drug addiction to include the biological basis for drug craving and relapse. In the next 10 years, it is expected that the biological mechanisms underlying euphoria, craving, relapse and other effects of drugs on the brain will be sufficiently understood to allow scientists to develop new medical therapies to treat drug addiction. Part of this understanding will come from computer-based programs that elucidate the relationships between receptors in the brain and abused drugs as well as potentially beneficial medications.

Investigators will build on the growing foundation of information about brain-drug interactions to develop medications, techniques and approaches that can be utilized to:

- block the effects of abused drugs;
- reduce the craving for abused drugs;
- reduce the withdrawal effects of drug addiction;
- reverse the toxic effects of abused drugs;
- develop substitutes for abused drugs with less toxic effects; and
- prevent the initiation of drug use.

In addition, novel approaches to treating addiction will be explored. For example, researchers will investigate the possibility of utilizing the characteristics of the blood-brain barrier in such a way as to prevent

abused drugs from getting into the brain. The maternal-fetal unit will be studied to see if medications can be developed that will decrease the mother's addiction while exerting little or no effect on the fetus.

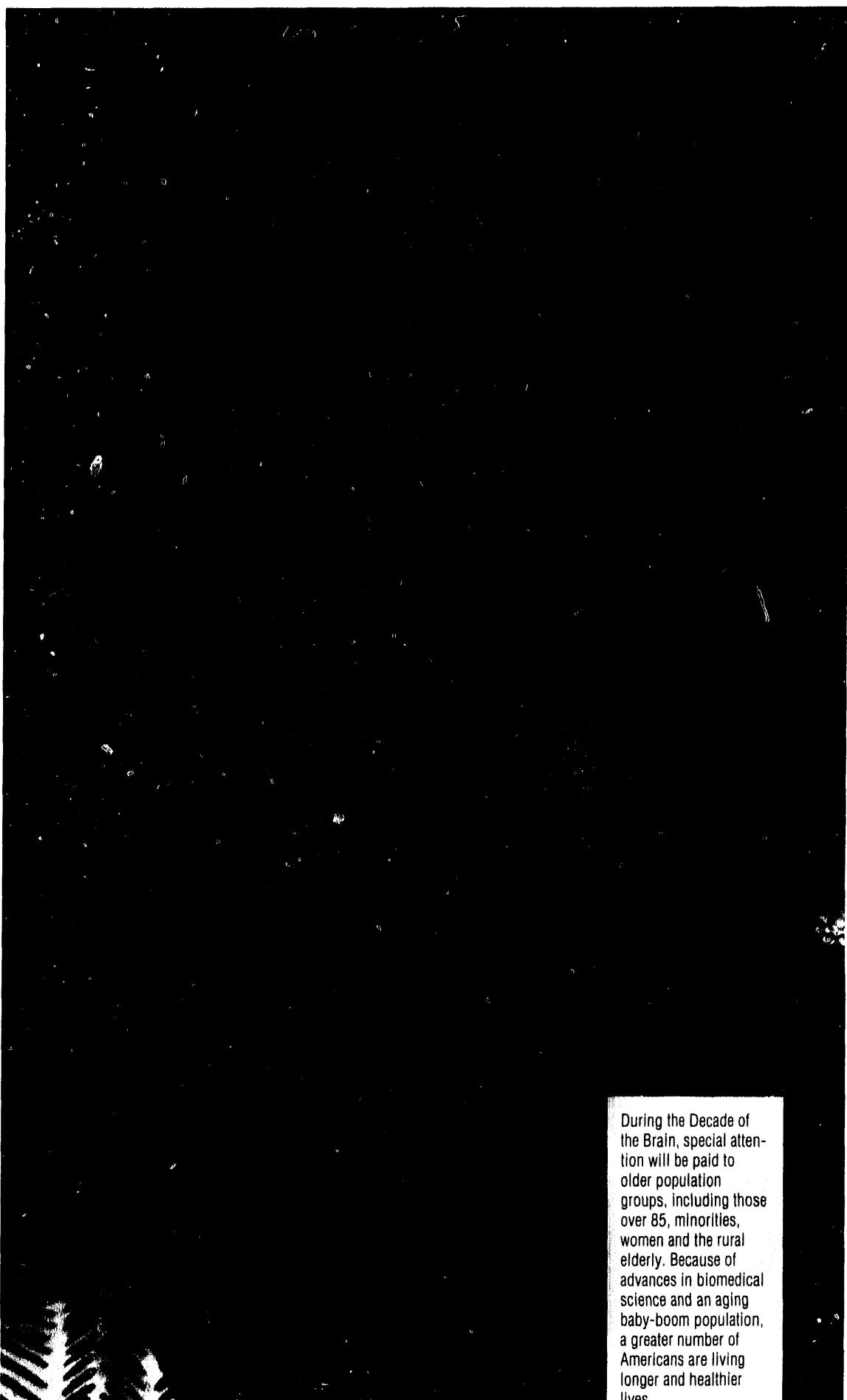
Drugs of abuse also have toxic effects that are not necessarily related to their addictive qualities. This requires further study. Abused drugs can interfere with important cognitive processes such as learning and memory, and some drugs produce long-term, and sometimes permanent, brain damage. Certain drugs may also destroy specific types of nerve cells, possibly resulting in premature onset of certain neurological disorders such as Parkinson's disease. In addition, investigators are beginning to delineate the devastating effects abused drugs can have on development.

During the next decade, investigators will also address questions related to genetically determined vulnerability to drug abuse. Particular attention will be focused on the effects of drug exposures on the brain and nervous system in high-use individuals.

One of the major issues that must be considered in developing effective treatments for addictive disorders is comorbidity—the coexistence of substance abuse with other health problems, such as mental disorders. People with drug or alcohol abuse disorders are seven times more likely than the general population to have a history of mental disorders. Among those with an alcohol abuse disorder, 37 percent also had or have a mental disorder, and 53 percent of those with a drug abuse disorder had or have a mental disorder.

During the Decade of the Brain, researchers will expand and improve epidemiologic survey techniques to better understand the relationship between substance abuse and mental disorders. Research efforts will focus on understanding the basic, biological relationship of addictive disorders to mental disorders, and on developing treatments that take into account the presence of both disorders. Scientists will work to determine if there is a genetic link between the development of substance abuse and other brain and behavioral disorders, or if comorbidity is related to environmental factors. For example, attention deficit disorder, or hyperactivity, in adults may lead to antisocial behavior that results in social isolation. This may in turn lead to substance abuse. Likewise, the use of certain drugs may alter chemical systems in the brain, resulting in disorders such as depression or attention deficit disorder. Alternatively, the comorbidity of these disorders may have a genetic component that results in genetically determined disturbances in similar neurotransmitter systems.

Scientists will also work to develop specific pharmacological interventions for substance abuse and mental disorders that do not compromise the treatment of the concurrent disorder, or make it worse. In addition, investigators will continue to determine the best mode of treatment when both disorders are present. Efforts to develop effective treatments will be greatly facilitated by a fundamental understanding of the neurotransmitter systems involved in each of these disease categories.



During the Decade of the Brain, special attention will be paid to older population groups, including those over 85, minorities, women and the rural elderly. Because of advances in biomedical science and an aging baby-boom population, a greater number of Americans are living longer and healthier lives.

Aging and the Human Brain

A major shift in age distribution is taking place in this country. Advances in biomedical science, coupled with an aging baby-boom population, now allow a greater number of people to live longer and healthier lives. By the year 2000, an estimated 13 percent of the U.S. population will be 65 or older. At the same time, however, the incidence of degenerative brain disorders such as Alzheimer's disease and Parkinson's disease is steadily increasing.

Brain function in the later years has long been of interest to the lay public as well as the research community. Contrary to popular belief, major declines in cognitive abilities and "senility" do not accompany advanced age in the absence of illness. Cognitive processing may be slowed but seldom becomes an impossible task for healthy older people. Certain functions such as vocabulary retrieval can even improve. Among the many age-related disabilities that lead to institutional care, those related to changes in brain functioning have the most significant implications for public policy and priorities for further research. Failure in cognitive functioning is one of the principal causes of institutionalization of older people. In addition, changes in the brain affecting sensory, motor and cognitive functioning have a profound influence on the quality of life of older individuals.

■ Accomplishments

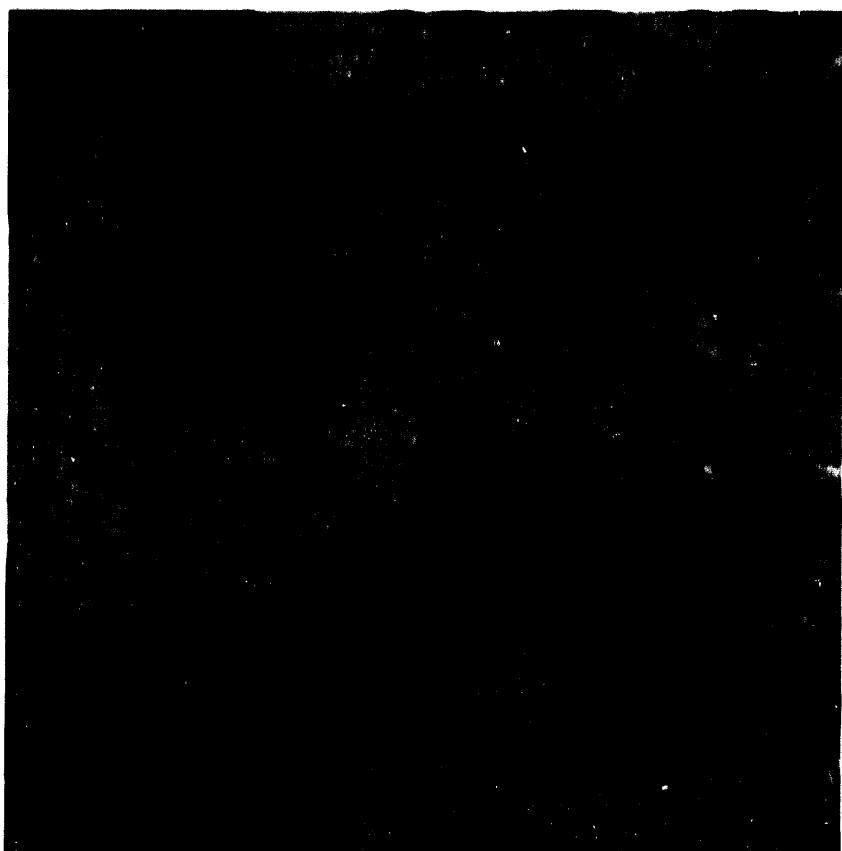
Alzheimer's Disease and other Dementias. Dementia afflicts 10 percent of people over 65. Dementia is the loss of the ability to learn new information and to recall and use previously acquired knowledge effectively. It is the final product of a variety of disease processes. In the elderly, Alzheimer's disease is a prominent cause of dementia, but it is becoming increasingly evident that it is not the only one. As our population ages, the incidence of dementia will increase. Of those over 85 years of age, studies show that as many as 50 percent will be impaired by dementia. This translates into a cost of well over \$90 billion per year spent on the care of people with dementia in homes, hospitals and long-term care institutions. Four issues are focal points for current research on Alzheimer's disease and other dementias: identifying the underlying causes of these disorders; identifying and understanding the pathological changes that occur in the brain; developing accurate diagnoses; and finding effective treatments.

The search for the cause of Alzheimer's disease has focused on the role of genes, toxins, infectious agents, head trauma and stress, as well as changes in the immune system, the endocrine system and normal metabolic processes. Scientists are looking at each of these factors as a possible cause of the disease, either alone or in combination.

Other investigators are exploring the possibility that the risk of Alzheimer's disease might be increased by age-related changes in healthy brain tissue.

The identification of genetic and biological markers for Alzheimer's disease will help clinicians make an early, accurate diagnosis of the disorder. Researchers have located an area on chromosome 21 that may be linked to the early onset of the familial form of the disease. The protein, amyloid, that accumulates in plaques in the brains of Alzheimer's patients is regulated by chromosome 21. Currently, scientists are investigating whether amyloid deposits are causally related to Alzheimer's dementia or whether they represent an unsuccessful attempt by the brain to defend itself against damage done by other toxic factors or pathological processes.

The characteristic folds of the human brain are abnormally wide in this Alzheimer's disease patient, because brain cells have died in the course of disease.



Advances in PET, single photon emission tomography and MRI have helped scientists identify and track over time the structural and functional alterations in the brain as dementia progresses. Alzheimer's disease can be discriminated from other dementias on the basis of visualized changes in nerve receptor distributions and density. Experimental testing offers promise for improved diagnostic accuracy and earlier diagnoses.

Early and accurate diagnosis of Alzheimer's disease has already had a major impact on the progress of research on dementia. In older people, the disease is difficult to diagnose in its early stages, and it is sometimes mistaken for other kinds of dementias and mental diseases. Incorrect diagnosis is thought to be common, perhaps ranging from

10 to 30 percent in the general medical population. Currently, definitive diagnosis can be obtained only through the examination of brain tissue.

There is no effective method of prevention, treatment or cure for Alzheimer's disease. However, recent research findings indicate the potential for use of nerve growth factor in treatment. The application of transgenic and implant technologies to research provides exciting prospects for treatments including the direct implantation of altered neurons that could synthesize and secrete brain transmitters or express receptors where they are needed in the brain. The search for growth factors and other biochemical determinants of neural growth, development and regeneration could provide new pharmacologic approaches to the therapy of degenerative diseases. In addition, there are a number of new drugs that are strong candidates for clinical trials.

A potential animal model for Alzheimer's disease recently has been identified in aged primates with an abnormal brain-cell feature—the neurofibrillary tangle. Last year a 34-year-old monkey with impairment of spatial memory and learning disabilities was reported to have neuritic plaques and neurofibrillary tangles upon autopsy. These findings emphasize the importance of continuing the study of aged primates as animal models for Alzheimer's disease.

Parkinson's Disease. The frequency of Parkinson's disease increases markedly after age 50. Consequently, the increasing number of older people in the United States has led to an increase in the number of people who are developing parkinsonism. There are now perhaps 500,000 people with the disease in the United States. Parkinson's disease is a progressively disabling neurologic disorder caused by the degeneration of dopamine-producing nerve cells that originate in an area of the brain called the substantia nigra. Tremor, rigidity, undirected movement, impaired dexterity and postural instability result, often accompanied by dementia and behavioral abnormalities.

A major advance in the treatment of Parkinson's disease was the introduction of levodopa therapy. This drug has permitted thousands of elderly patients to live productive lives for one or two decades longer than was previously possible. Unfortunately, patients receiving levodopa over a long time often eventually suffer undesirable side effects and a loss of therapeutic effect. New approaches under study include surgery, new drugs and new drug-delivery systems.

This past year a clinical trial revealed that treatment with the drug deprenyl delays the progression of symptoms in patients with early Parkinson's disease and postpones the need for levodopa therapy. This is the first time a drug has been developed that can slow the progression of a neurodegenerative disease. Deprenyl was also found to increase significantly the time patients remained gainfully employed, a benefit that will yield hundreds of millions of dollars annually in increased productivity and annual savings in health care costs.

Vision Disorders. Three age-related disorders of the visual system—macular degeneration, glaucoma and cataract—are major causes of blindness and visual disability, affecting millions of Americans. The

development of laser photocoagulation therapy, other new surgical procedures and new drugs has revolutionized treatment of these conditions.

Hearing Impairments. One-third of persons over 65 have a hearing loss sufficient to interfere with speech perception and effective communication, and the prevalence rises with increasing age. The inner ear is primarily affected, although auditory nerve and brain stem degeneration probably also contributes to hearing disorders. Recent work has demonstrated that with advancing age, certain neurotransmitters are depleted in some brain structures but not in others, suggesting that some age-related hearing problems might be reversed or prevented in the future by correcting neurotransmitter imbalances.

■ Future Plans and Potential Benefits

Alzheimer's Disease. Major research opportunities exist for studies on the cause, diagnosis and treatment of this disease. If, as recent research suggests, amyloid plays a critical role in neuronal death, and chemicals known as tachykinin peptides block amyloid toxicity, then a new Alzheimer's therapy suggests itself. Further research on the mechanism of amyloid formation and amyloid neurotoxicity and the role of tachykinin peptides in the brain is likely to yield significant results.

Animal studies of skin fibroblast cells implanted into injured areas of brain may one day lead to treatment for people with central nervous system degeneration. Before implanting fibroblasts, scientists genetically modify the cells to secrete nerve growth factor. Animals with the modified implants have less nerve cell degeneration and demonstrate enhanced sprouting of the axon portion of nerve cells. Though clinical applications require much further study, these results are encouraging. Growth factors and neural tissue implants, both resulting from molecular technologies, offer new methods of improving brain function.

Other avenues being explored focus on highly selective neurotransmitters that promise to directly influence functionally deficient nerve receptors. Using recombinant DNA probes, neurotransmitter systems and familial inheritance patterns will be determined, and genetic engineering methods will be applied to the development of biologically active molecules for use in treatment.

There is an immediate need for improved diagnostic screening for Alzheimer's disease. However, its diagnosis and screening will continue to be difficult and sometimes inaccurate until a better understanding of the normal aging process is achieved. The major difficulty in diagnosis involves the definition of the disease itself and its varied and, at times, subtle manifestations. Alzheimer's disease remains a combined clinical and pathologic diagnosis. A continuing effort to define the disease precisely and to develop methods of definitively distinguishing Alzheimer's disease from other nervous system diseases must remain the subject of intense research. Meanwhile, the potential for identifying genetic and other biological diagnostic markers is promis-

ing. Advanced imaging techniques with EEG and PET will assist in these studies by showing the changes in brain structure and metabolism during the course of Alzheimer's as well as Parkinson's and Huntington's diseases.

Parkinson's Disease. It has been shown that a synthetic drug, MPTP, produces parkinsonian disorders in non-human primates and other animals as well as in man. These models are being used to explore the use of new implantation techniques which can replace or regenerate the cells damaged in Parkinson's disease and restore healthy function. It is likely that cells from tissue cultures, including those from genetically engineered nerve cell lines, will prove useful in obtaining a more functionally effective transplant.

For both Alzheimer's and Parkinson's diseases the following population studies are planned:

- Epidemiologic studies will identify disease risk factors for Alzheimer's disease with attention to subgroups defined by age, sex, race, ethnicity, socioeconomic status and urban/rural setting.
- Studies of precursors (e.g., dietary, medical, occupational, residential, environmental) to Parkinson's disease will determine whether they predict the later development of Parkinson's disease (e.g., consuming foods with a high vitamin E content may protect against Parkinson's disease). Similar studies may be performed with those who develop amyotrophic lateral sclerosis and Alzheimer's disease.

New areas of promising research on the sensory systems include:

Vision. In a group of diseases called glaucoma, elevated pressure in the eye leads to irreversible damage to the optic nerve and consequent blindness. The most common form affects many people aged 70 or older. Drug, surgical or laser treatment of glaucoma often can relieve the elevated intraocular pressure and thus prevent or slow optic nerve damage, but it is impossible to determine which individuals are at risk for eventual visual loss. Discovery of ways to detect glaucoma at its very earliest stages, before nerve damage occurs, is important. New studies on the cause and prevention of cataracts are also needed.

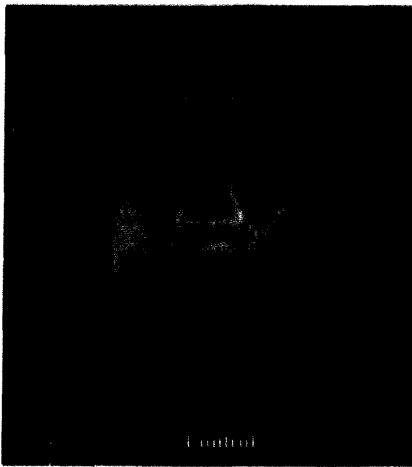
Hearing. The issue of hearing impairment associated with aging (presbycusis) is complex and includes central as well as peripheral auditory features. New findings of changes in auditory system anatomy with aging suggest new directions in restorative interventions. Other research results indicate that, even in those older adults who show no signs of peripheral hearing loss as measured by intensity discrimination, frequency discrimination and duration discrimination tasks, there can be significant decline in measures of central brain functions, such as correct temporal ordering and sequencing of speech sounds. This finding suggests that further research on central brain mechanisms may lead to new methods of reducing hearing impairment in older adults.

Taste and Smell. The relationships between food preference, appetite and satiety, and the ability to taste and smell in the elderly are poorly understood. These relationships have implications for the nutritional status of the elderly. Future research opportunities include the study of variability in how well the elderly taste and smell, and the location of brain lesions responsible for olfactory loss in the elderly.

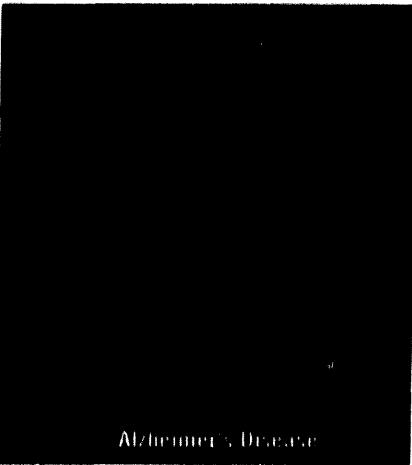
Other emerging areas of research opportunity include:

Sleep Disorders. Since a majority of elderly individuals experience disturbances in normal patterns of sleep, research in this area is important. New methodologies now permit better documentation of the natural history of certain sleep disorders and of associated underlying pathophysiology in the aging brain, pointing out new research directions for clinical intervention.

Scientists at the National Institute on Aging use PET to study changes that occur in the brain of patients with Alzheimer's disease. The PET scan on the bottom shows the dramatic changes Alzheimer's disease causes



Control



Alzheimer's Disease

Mental Disorders. The recognition of late-onset mental disorders (e.g., late-onset schizophrenia) gives scientists another perspective from which to study such disorders. The same applies to atypical depression in later life; suicide is especially common in elderly men.

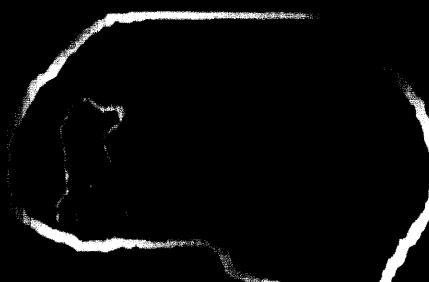
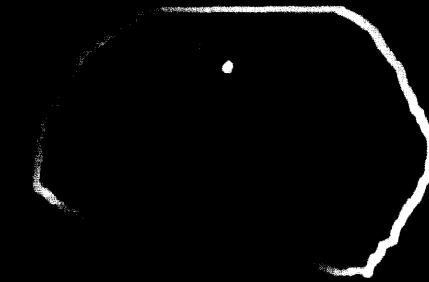
Alcohol Abuse. The effect of alcohol on central nervous system function is of critical concern in relation to its interaction with medication (e.g., in inducing delirium) and in its impact on cognitive performance (e.g., in causing automobile crashes). Further research could add to our understanding of alcohol-drug interactions and other effects of alcohol on the aging brain.

Neurotoxins. Research on the influence of neurotoxic substances on aging processes has only recently begun. As a consequence, considerable effort needs to be focused on determining the influence of neurotoxic substances on aging processes.

Falls. The frequency of falls—a major cause of hip fracture leading to institutionalization in elderly Americans—can be reduced through research on the central nervous system. Such studies could focus on risk factors relating to the influence of decrements in visual

and vestibular systems and to the nervous system effects of medications and alcohol in association with falls.

In all of the above promising areas of research, attention will be paid to special, older population groups, including the old-old (those over 85), minorities, women and the rural elderly. Research on aging builds upon the increasing recognition that much of the decrement in later life represents the impact of disease rather than the normal concomitants of aging. This research builds, too, on the growing recognition that disorders and disabilities in older Americans can be modified.



Research with modern imaging techniques, such as PET, is yielding new maps of where and how the brain processes information. Above, computerized images of PET scans show increased blood flow to human brain areas activated while hearing, seeing, speaking, or thinking about the meaning of a word.

Human Behavior and Mental Disorders

The brain interacts with the world through behavior. Just how do the properties of the human nervous system affect an individual's behavior, and vice versa? This question is increasingly important as scientists and clinicians consider promising new therapies and interventions that target the nervous system to address formidable problems of mental and physical health. These emerging and future treatments are made possible by new technology, new scientific techniques, and a vast improvement in our understanding of the human brain and nervous system.

Mental illness and other behavioral disorders are highly stigmatizing, socially disruptive and economically draining—in 1988 alone behavioral disorders cost the nation almost \$130 billion. Development of effective treatments would therefore improve not only the lives of those with mental disorders and their families, but also the economic productivity of the nation. Scientists are now gaining some insight into the bases of historically intractable diseases like schizophrenia and developing treatments for depression and other devastating mental illnesses. Knowledge concerning the actions of neurotransmitters, hormones and small peptides may lead to an array of effective, new treatments. A better understanding of childhood development may lead to early detection of physical, emotional or behavioral problems (such as violent behavior) and mental illness or its precursors.

■ Accomplishments

Schizophrenia. Roughly 2 million Americans suffer from schizophrenia. This disease strikes at the prime of life (often beginning in late adolescence) and has a large economic impact on the nation. Recent years have seen major developments in what has long been largely a mysterious disease. During the 1950s the first drugs with anti-psychotic properties were identified. Animal studies indicated that an important common factor for the drugs effective in schizophrenia was that they decreased dopamine action by occupying dopamine receptors. As a result, more specific antipsychotic drugs were developed and many are effective in treating more than 70 percent of those with schizophrenia. Recent research on neurotransmitter receptors in animals suggests that at least three classes of receptors for dopamine may play a role in psychosis and mediate the effects of some antipsychotic drugs. The three receptors have recently been isolated and their genes cloned.

Investigation of brain abnormalities in schizophrenia and other disorders has progressed rapidly with the development of new brain imaging technologies that allow the direct observation of brain activity.



PET allows study of dopamine and other neurotransmitter receptors in the brain tissue of living subjects with schizophrenia. MRI scans complement the PET scan data by providing detailed anatomical pictures of brain structures. Some of the most advanced scanning techniques have been used to study pairs of identical twins—one with schizophrenia and one without—and have revealed abnormalities in brain structure and function in the schizophrenic twins but not in the normal twins, suggesting that environmental or developmental factors, as well as genetic factors, are involved in the development of schizophrenia.

Depression. Approximately 15 million Americans will experience a major depressive illness in their lifetimes. Perhaps 50 percent of the nearly 30,000 suicides each year are due to depression—this is particularly true in teenagers and the aged. Like schizophrenia, depression reflects a delicate interplay between environmental factors and biological (both genetic and non-genetic) factors. A role for genetic factors in depression and other affective disorders is supported by twin and adoption studies, and enthusiasm for the application of molecular genetic techniques to the problem has increased recently following preliminary reports of gene linkages in bipolar (manic-depressive) disorder. On the other hand, an environmental event (e.g., family crisis, job loss or physical injury) can act as a triggering event for a major depressive episode.

New diagnostic approaches that combine tools of clinical science, molecular biology, neuroimaging and neurochemistry have yielded evidence of specific abnormalities in depression. These tools have also shown that there are many categories of these mood disorders, including the newly described seasonal affective disorder that is related to seasonal changes in the amount of daylight. Current research indicates that about 80 percent of those showing symptoms of depression can be effectively treated with antidepressant medications, bright lights or other therapies.

Childhood Development. It is estimated that 12 percent of all children and adolescents suffer from various mental disorders that severely impair their intellectual, emotional, social and familial functioning. Research over the last two decades in developmental neurobiology and genetics is paving the way for understanding the molecular and neurobiological bases of childhood behavioral disorders. Animal studies on the behavioral and physiological consequences of selectively disabling certain neurotransmitter systems, such as the dopamine system, may shed light on conditions such as attention deficit disorder and Tourette's syndrome. Additionally, the refinement of diagnostic criteria for behavioral disorders, the development of genetic linkage studies, and observations of hereditary bases for certain behavioral disorders are opening the way for identifying particular genes associated with behavioral disorders. Autism, for example, is a developmental disorder for which neurotransmitter studies show elevated serotonin levels, PET and electrophysiology scans show functionally impaired interactions between brain regions, and genetic studies reveal the disorder's association with the X chromosome.

Alcoholism and Drug Abuse. Scientists are examining all aspects of the complex circuitry of the brain to identify the causes and consequences of behavior associated with alcoholism and drug abuse. Genetic linkages to alcoholism have been found in studies with animals and humans, and there is growing evidence that children and other relatives of alcoholics are at higher risk for developing alcoholism than the general population. To aid in identifying those individuals who may have a genetic predisposition to abuse of alcohol, researchers have begun to identify multiple biological and behavioral markers that may underlie differences in vulnerability to alcohol abuse. Some of these markers exist in people with a family history of alcoholism but who have never themselves been exposed to alcohol.

Basic Behavioral Research. Basic studies of behavior expand upon and provide clues to guide further basic neuroscience investigations of brain mechanisms. One example derives from the common notion that we remember virtually nothing from infancy. The concept of "memory-updating" is the result of developmental studies that indicate that an infant's memories are highly enduring, even at 2 and 3 months of age, as long as new learning does not interfere. What remains in the infant's active memory is a function of how recently the learning occurred and what has been attended to, or learned, in the intervening period of time. Learned experiences quickly lose their usefulness in infancy—experiences that were functionally useful to the immobile infant at 2 months are no longer relevant, hence not remembered, when sitting-up or crawling begins. Efficient information processing requires the infant to retain only the most relevant and useful information. It appears that if the memory is "updated," the system is cleared of all irrelevant information. Nature thus has set up the learning and memory system of the infant for capabilities that reflect the needs of the early months of life. A search for the neuronal correlates of "memory-update" will be integrated into studies on the cellular basis of learning and memory.

Other Research. In the past, the neural and endocrine systems were considered to be interactive but separate. This distinction has now become blurred, partly because hormones and small peptides are now known to be chemical messengers that can amplify or dampen the action of nerve cells. Modern molecular tools have led to the discovery of such hormones and peptides in the brain. These messengers are often found in the same neurons as the classical neurotransmitters. The very recent cloning of the genes that encode the steroid hormones should advance studies on the action of steroid hormones in the nervous system.

■ Future Plans and Potential Benefits

Studies on behavior are highly complex, requiring multidisciplinary approaches combining clinical expertise, behavioral and systems analysis, expertise in cellular and molecular biology and neuroimaging technology. Scientists are now beginning to integrate such seemingly disparate approaches and aim, at last, for a greater understanding of how the interplay of environmental and biological factors contributes to behavior and cognition.

High-priority areas for future research include the following: 1) clarifying the genetic mechanisms associated with synaptic transmission between neurons, including the identification of genes that encode molecules involved with synaptic transmission and their regulation; 2) increasing understanding of the synthesis, degradation, activation and regulation of the various classes of neurotransmitter receptors; 3) identifying and characterizing genes associated with behavioral disorders; 4) establishing strong theoretical bases for the behavior of single neurons and neural networks; 5) understanding the neural mechanisms of thinking and emotion; and 6) identifying social and other environmental factors, including nutrition, that can modulate brain function across the life span.

The recent discovery of methods to grow nerve cells in culture should markedly improve approaches for asking questions about how nerve networks form, develop, process and retrieve information. Such research could enrich the theories of cognitive development and thereby stimulate important new questions about how the relationship between brain and behavior is established.

Research during the next decade will be aimed at identifying people who are genetically predisposed to developing mental illness, isolating the environmental factors that may trigger disorders such as schizophrenia, and defining the conditions in which those triggers operate. Basic investigations will be directed toward understanding the pathophysiology of the dopamine and serotonin neurotransmitter systems and how the environment interacts with them. Studies aimed at characterizing and cloning brain receptors will help clarify the basic abnormalities underlying schizophrenia and the mechanisms by which antipsychotic drugs act. These studies may lead to the design of more effective medications with fewer side effects.

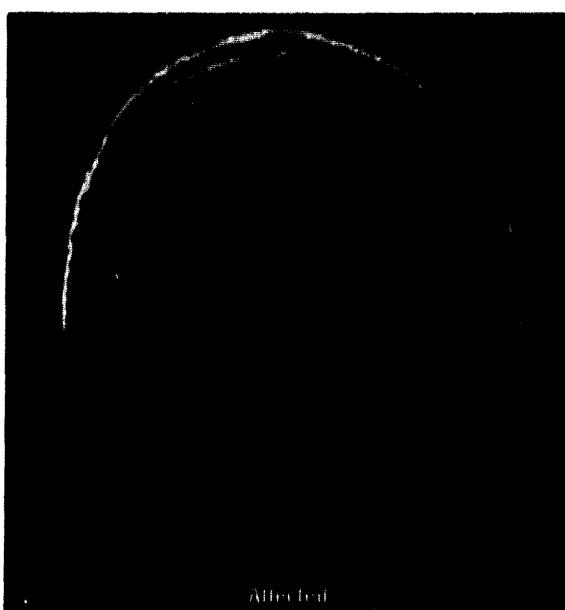
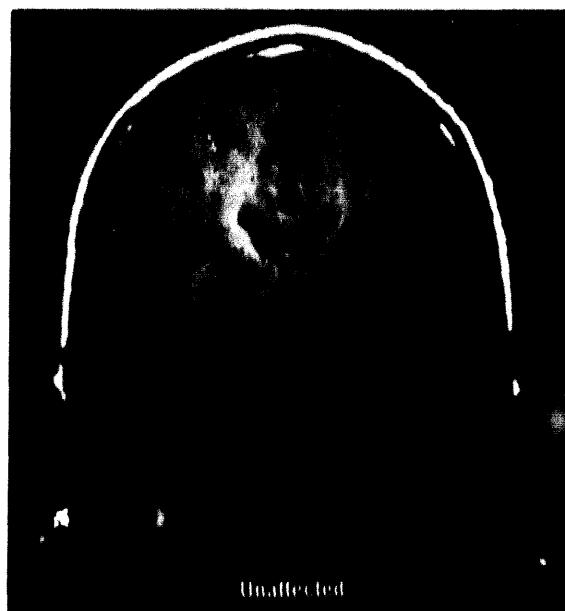
Research on the roles of the neurotransmitters serotonin and norepinephrine in mental disorders will focus on the molecular biology of neurotransmitter receptors, second messenger systems, and changes in neuronal function over time. Clinical research is directed to the development of accurate diagnostic instruments that can differentiate among the types of depression. Biological markers—including genetic markers—and neurological and biochemical tests will be sought in order to more accurately separate primary depressions from those associated with drug and alcohol abuse, Alzheimer's disease and other disease states. With this information, optimally effective treatments will be developed for each diagnostic group. Some of these treatments are likely to be pharmacological; others will influence brain systems through alternative mechanisms such as diet or light exposure. Investigators will seek to understand the mechanisms of action of traditional antidepressant and anti-manic-depressive drugs, including lithium, in the hope of developing even more efficacious medications with fewer side effects.

Scientists will seek new therapeutic medications for depression and other behavioral disorders. For instance, peptides that interact with corticotropin-releasing hormone or the thyroid-stimulating hormone receptor—neither of which was thought to be involved in depression several years ago—are currently being studied to find new compounds that achieve effective antidepressant activity. Future research on the

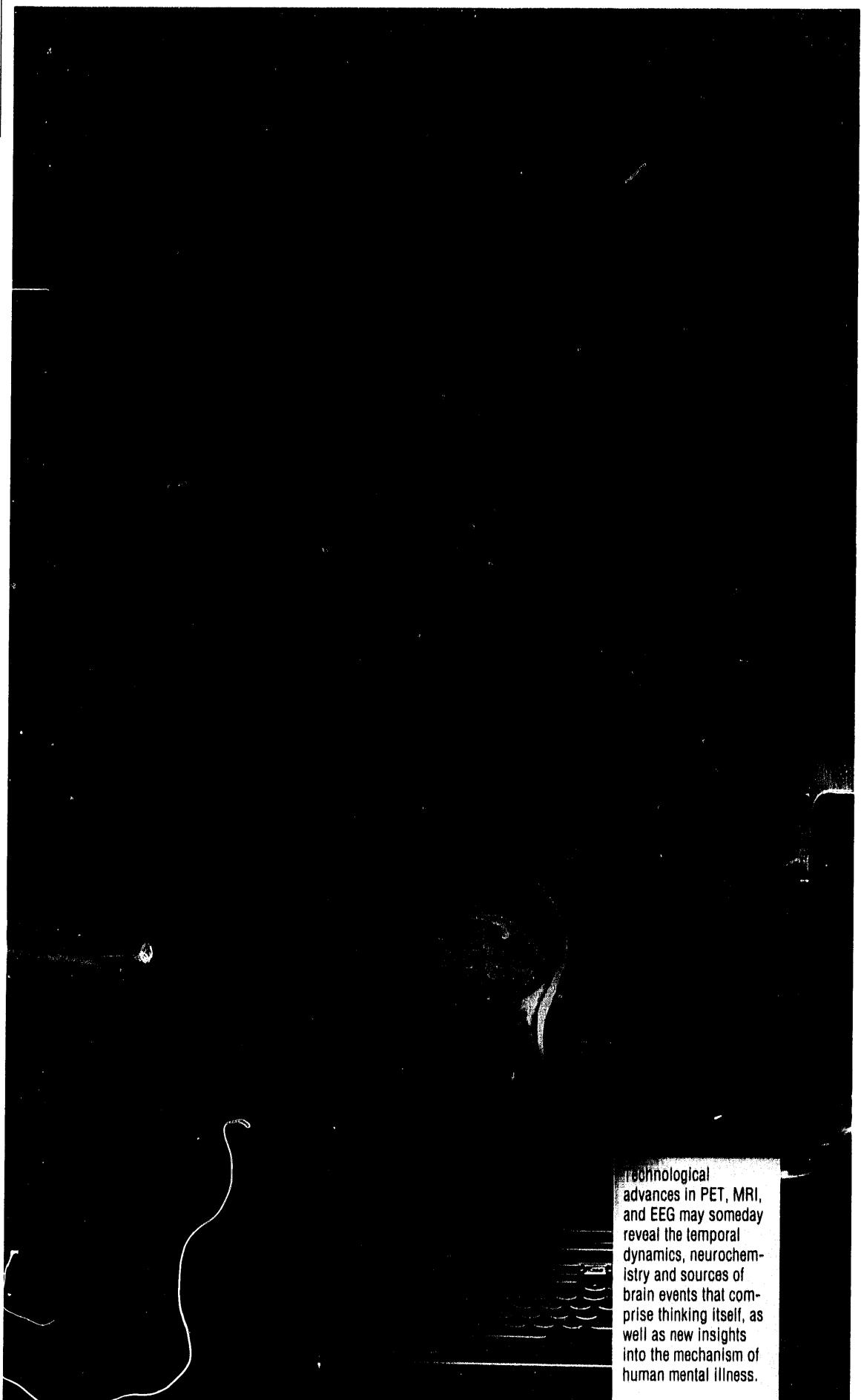
relationship between the various chemical messengers will provide insight into their functional role. There is a great need to know more about how peptides and hormones affect particular behaviors. Researchers need to know where they act and how they mediate their effects on brain tissue. An understanding of how such agents work could create a vast reservoir of ideas for new therapies for modifying behavior.

Future studies on childhood behaviors will address the following issues: 1) What are the genetic factors underlying the susceptibility of some people to environmental challenges? 2) What are the brain mechanisms through which specific environmental events early in life modify the development of these different behavioral patterns? 3) What are the long-term health and behavioral consequences of extreme reactivity to environmental challenge early in life, and can the early patterns of response be modified in adulthood?

Another promising area of research concerns the development of brain lateralization and how this mechanism is linked to the acquisition of language in children. Advances in this area are likely, due to the availability of new analysis techniques for brain-evoked responses that have been generated in normally developing children. This research could help in the diagnosis of language abnormalities. Progress during the decade is also probable on the question of how stimulating environments, early in life, can help shape brain functions that may influence a child's cognitive development. Advances in this field of research could have important benefits for babies born at risk for language and other developmental disabilities. If new knowledge could allow the identification of optimal environmental stimulation, then procedures for early intervention could be implemented.



Studies using MRI are uncovering abnormalities in the brains of schizophrenics. These MRI scans of identical twins show enlarged brain ventricles (arrows) in the schizophrenic twin compared to the unaffected twin. Since identical twins possess identical genes, these structural differences suggest that environmental, not genetic factors, trigger schizophrenia. (Photos courtesy of the National Institute of Mental Health.)



Technological advances in PET, MRI, and EEG may someday reveal the temporal dynamics, neurochemistry and sources of brain events that comprise thinking itself, as well as new insights into the mechanism of human mental illness.

Violent behavior not only claims the lives of over 20,000 Americans each year, but the threat of violence severely detracts from the quality of life in communities across the country. The development of effective strategies to prevent deaths and injuries resulting from violent behavior depends in part on our understanding of the determinants of violent behavior that are associated with childhood development. Research is needed to determine which childhood exposures and behaviors are associated with future violent behavior, and which interventions are most effective and developmentally appropriate to reduce the effects of harmful exposure or to modify factors found to be predictive of violent behavior.

The clarification of brain mechanisms that underlie cognition is likely to be particularly fruitful in the coming decade. Technological advances in such areas as PET, MRI, MEG and EEG, that permit imaging of dynamic aspects of brain function, will reveal the temporal dynamics, neurochemistry and sources of brain events that comprise thinking itself. The use of these technologies to evaluate human functioning combined with new insights from animal and computer models should ultimately provide the bases for a fuller understanding of the mechanisms of human mental illness.



This MRI scan showing a bullet in the brain was provided by the Centers for Disease Control, whose agenda includes research and programs aimed at prevention, treatment and rehabilitation of both unintentional and intentional head injuries.

Brain and Spinal Cord Damage

Spectacular as the progression of neuroscientific knowledge has been in recent decades, it cannot yet relieve the burdens that encumber many patients with neurological disorders. Middle-aged and elderly men and women with Parkinson's, Huntington's and Alzheimer's diseases still suffer as these disorders rob them first of their minds and bodies and then of their lives. This same age group finds itself at increased risk of stroke and brain tumors. Youngsters still face devastating disorders such as Gaucher's and Batten's diseases. People in their most productive years still are afflicted with traumatic injury of the brain and spinal cord, multiple sclerosis and epileptic seizures, disorders that can damage family relationships, self-esteem and economic well-being. Within the next 10 years, the causes of many brain disorders could well be identified, including those for amyotrophic lateral sclerosis; Alzheimer's, Huntington's and Parkinson's diseases; autism; and multiple sclerosis. Better treatments for these afflictions are a real possibility in the decade to come. Further progress depends on a broad-based research and research-training effort, uniting basic and clinical studies, and taking full advantage of newly developed technologies that have already given promise of success. Increased research training is essential to capitalize on investments already made and to encourage young scholars to pursue research careers. Exciting new discoveries, instrumental to improving the nation's health, are within grasp.

■ Accomplishments and Future Opportunities

Traumatic Brain and Spinal Cord Injury. Trauma to the central nervous system is a major public health problem and the focus of significant research efforts. Over 2 million people suffer head injuries each year, and of these approximately 100,000 die and 500,000 require hospitalization. Motor vehicles cause half of all traumatic brain injuries, falls cause 21 percent, and some 12 percent are the result of assaults or other violent acts. Each year, 5,000 survivors of traumatic brain injury develop epilepsy. The economic costs of brain injury approach \$25 billion per year. Spinal cord injuries have permanently paralyzed approximately 250,000 Americans. In addition it is estimated that there are over 13,000 hospital admissions each year due to spinal cord injuries. Even without permanent damage, those who survive severe brain and spinal cord injury typically need 5 to 10 years of intensive medical treatment and rehabilitation services.

The prevention of brain and spinal cord injuries is also important. In states with motorcycle helmet laws, mortality rates due to neurological damage caused by motorcycle crashes are half those of states with partial or no helmet legislation. Programs are needed to increase the use

of helmets by motorcyclists and bicyclists. Biomechanics research is also needed to develop more effective helmets and determine the mechanisms of head and spinal cord injuries that result from motor vehicle crashes, sports activities and worksite incidents.

Vigorous intensive-care monitoring and early treatment in patients with head injuries have led to improved survival. In animal studies, scientists have discovered that a series of complex biochemical events that occur within the first 10 hours after brain injury appear to make the injury worse ("secondary injury"). As researchers develop methods to halt or retard such secondary injury, physicians will be able to reduce the ultimate severity of damage to the brain after injury. Investigators have also shown that damaged nerve cells in the central nervous system sprout new branches when they are in contact with supporting cells, demonstrating that adult brain cells have the capacity for repair and growth. Scientists need to investigate thoroughly how this property can be used to repair the injured brain.

Multidisciplinary, clinical research centers must develop the capability to pursue epidemiologic studies of patients with brain or spinal cord injury within local communities. Such centers should conduct clinical trials related to improved diagnosis and treatment of patients and should integrate laboratory research into these studies. In addition, the dysfunctional behavioral, cognitive and emotional responses of people with these injuries need to be thoroughly understood.

The outlook for patients with spinal cord injury has always been very poor, but it has improved. A multicenter clinical trial has recently demonstrated that very high doses of methylprednisolone, given within 8 hours of injury to patients with spinal cord injury, significantly

reduced the extent of neurological damage for these patients. The patients also showed improved sensory and motor function. Further improvements in the treatment of spinal cord injuries require that scientists understand the immune response, the action of inhibitory proteins, and the molecular mechanisms by which internal scars form at the site of injury. Genetically engineered cells might provide the next important step in spinal cord



regeneration. Medical researchers have already shown that transplants of unengineered cells survive, replicate and attempt to connect with existing tissue.

Infections of the Brain. There are more than 35 human infectious diseases that seriously affect the brain and nervous system. In the 1980s, four new infectious diseases appeared: AIDS, Lyme disease, tropical

spastic paraparesis syndrome and the spongiform encephalopathies. Their cure is one of the challenges of the 1990s.

Neuro-AIDS. AIDS appeared in the late 1970s, and the retrovirus that causes AIDS—HIV-1—now infects over 1 million Americans. More than 70 percent of AIDS patients suffer from neurological problems, which are the primary cause of death for many. HIV-1 has a predilection for cells of the nervous system and may seek these cells as a harboring place, causing latent infection. Patients with neuro-AIDS also have a markedly increased incidence of a type of rare brain tumor. Investigators are now trying to determine how the virus enters the brain through the usually impenetrable blood-brain barrier, how it damages nerve cells, and how it establishes long-term residence in the brain.

Lyme Disease. Caused by a microscopic spirochete and spread by tiny ticks, this disease creates a variety of chronic neurological disabilities that could be as devastating in the 1990s as syphilis—also spread by a spirochete—was in the 1890s. Already the disease is almost epidemic in various parts of the United States. Better methods are needed for the diagnosis and treatment of this disease.

Tropical Spastic Paraparesis Syndrome. This disorder occurs not only in the tropics, but also in the United States and other countries. It is characterized by a progressive difficulty with walking, and patients ultimately require a wheelchair. The causal agent of this disease is another retrovirus, HTLV-1, which was previously identified as a cause of human T-cell leukemia. The association of HTLV-1 with a chronic disease of the brain raises questions about the role of viruses in other chronic, neurologic diseases such as multiple sclerosis, Alzheimer's disease, Parkinson's disease and certain types of brain tumors. Scientists may answer these questions through new, extremely sensitive, molecular biological techniques.

Spongiform Encephalopathy. The agents which cause this disorder are unconventional viral particles. One of them, the scrapie agent, which was previously limited to sheep, has appeared as a major epidemic in cattle in the United Kingdom. Called "mad cow disease," it is a disease of the nervous system, and spread to a new animal species because infected sheep were used as an ingredient in feed. It has created an economic disaster for the British agricultural community. There are now fears that it could spread to humans also through food ingredients. These unconventional "agents" appear to be working by different disease mechanisms than those of the usual viruses. The mechanisms by which they spread, and possible approaches to their control, need to be aggressively pursued before epidemics such as mad cow disease spread to other animal populations, or conceivably to humans.

Epilepsy. Epilepsy is not a single disease but a group of different disorders affecting the brain with a common manifestation: recurrent, debilitating seizures. Approximately 2 million people in the United States have epilepsy, and 20 million Americans will have at least one seizure during their lives. Seizures are estimated to affect one of every 200 newborn infants in the United States, and are frequently the first indication of central nervous system damage. Mortality rates of 10 per-

cent have been reported from status epilepticus, which occurs when seizures persist for long periods or occur so frequently that there is no recovery between attacks. In many epileptic patients, the cause of the seizures has not been found. Seizures may be difficult to diagnose and, therefore, to treat.

About 70 percent of those who suffer recurrent seizures can satisfactorily control them. Current medications, however, do not adequately control the seizures of many of the 100,000 people who develop epilepsy each year. While newly developed drugs are effective for many patients, some types of seizures are resistant to drug therapy. In some of these cases, surgical therapy is now used successfully. Thanks to new imaging techniques that help determine the area of brain involved, surgery for epilepsy has become safe and, for well-selected patients, extremely successful. Experts estimate that 5,000 new patients in the United States are suitable candidates for surgery for epilepsy each year. There is a need for the further development of the surgical approach to epilepsy since only about 500 patients receive this therapy annually.

Despite the progress made in controlling epilepsy, very little is known about the causes of seizures. A major question is how the brain controls excitability of nerve cells. It is evident that some forms of epilepsy have a genetic basis. For instance, a normal cell can be transformed into an abnormally excitable cell by certain types of genetic manipulation. The technologies are now available for identifying the genes that may underlie these forms of epilepsy.

Seizures have long been associated with changes in behavior. Learning, attention and processing deficits have been well described in children with epilepsy. Many of these problems also persist into adulthood. Scientists must better identify, understand and develop specific therapies for the types of behavioral abnormalities seen in these conditions.

Stroke. Stroke (cerebrovascular disease) and stroke-related brain illnesses are the third leading cause of death in the United States. Furthermore, brain damage from stroke represents the largest single cause of neurologic crippling in the United States. Each year approximately 350,000 persons suffer a first stroke, and another 100,000 will have a recurrent attack. A fifth of these patients will die, and a third will remain permanently disabled. Stroke also is increasingly a major contributor to the late-life dementia that affects more than two-fifths of Americans over 80. Indeed, stroke is the most common cause of disability requiring rehabilitation, and the annual social and financial costs of stroke are well over \$25 billion. Implementation of the knowledge gained through research, including research on animals, has reduced stroke deaths in the United States by 50 percent. Now, however, stroke rates are climbing again, as is the resulting number of persons disabled by stroke.

Recently, anticoagulant drugs were shown to be highly effective in preventing certain forms of stroke. A major clinical trial showed that treatment with aspirin or warfarin greatly reduces the risk of stroke in patients with atrial fibrillation. General adoption of appropriate treatment regimens is expected to result in a reduction of 20,000 to 30,000 strokes each year. Clot-dissolving agents given at the onset of stroke have now been found to reduce the severity of the disease. In addition, the latest research points to several entirely new therapeutic

drug families that may for the first time provide specific drugs to prevent stroke or halt the tissue damage that devastates so many stroke-affected brains.

A major advance in stroke research is the discovery that there is a period of time immediately after the injury during which neurons surrounding the area of the lesion are sick, but still alive. Recent research shows that, although the major brain damage occurs within the first few hours after stroke, injury to cell groups controlling important cognitive functions such as memory continues for as long as 2 days. This may provide a therapeutic "window of opportunity" during which brain damage may be limited. Intensive effort is directed toward discovery of the critical parameters for survival and the best approaches to salvage those vulnerable neurons. New research needs to be directed toward developing effective medical interventions and evaluating the surgical techniques now widely used. Also needed is research to achieve a better understanding of the brain's potential for regeneration and a search for agents to stimulate this process. Such agents also should facilitate the successful transplantation of young brain cells into areas of damage in order to hasten recovery. Research on animals will play a critical role in those basic studies.



We must continue to stress stroke prevention. Far more lives will be saved by preventing this disease than by treating it. We must design studies to evaluate the long-term effects of complex prevention programs. Additional stroke risk factors—especially those in which intervention may be possible—must be identified in order to continue advances in stroke prevention research; this is particularly important for populations at high risk of stroke, such as blacks and the elderly.

Brain Tumors. Brain tumors are the second most common malignancy of childhood. There is a second incidence peak at the age of 55, causing more than 35,000 deaths a year. Scientists are conducting new research on the specific genetic codes that regulate brain cell growth and the balance of growth-controlling factors, and considerable progress has been made in understanding brain tumors.

Brain tumors show highly variable degrees of invasiveness, with different rates of progression and biologic activity found in tumor sites growing adjacent to each other. The development of systems to directly slow the metabolic activity of tumors is now considered possible. Future research must also focus on the genetic markers that define the

Dr. Lewis P. Rowland of Columbia University tests fine motor control in a woman with amyotrophic lateral sclerosis, a progressive and usually fatal disease in which the nerves and muscles for voluntary movement degenerate.

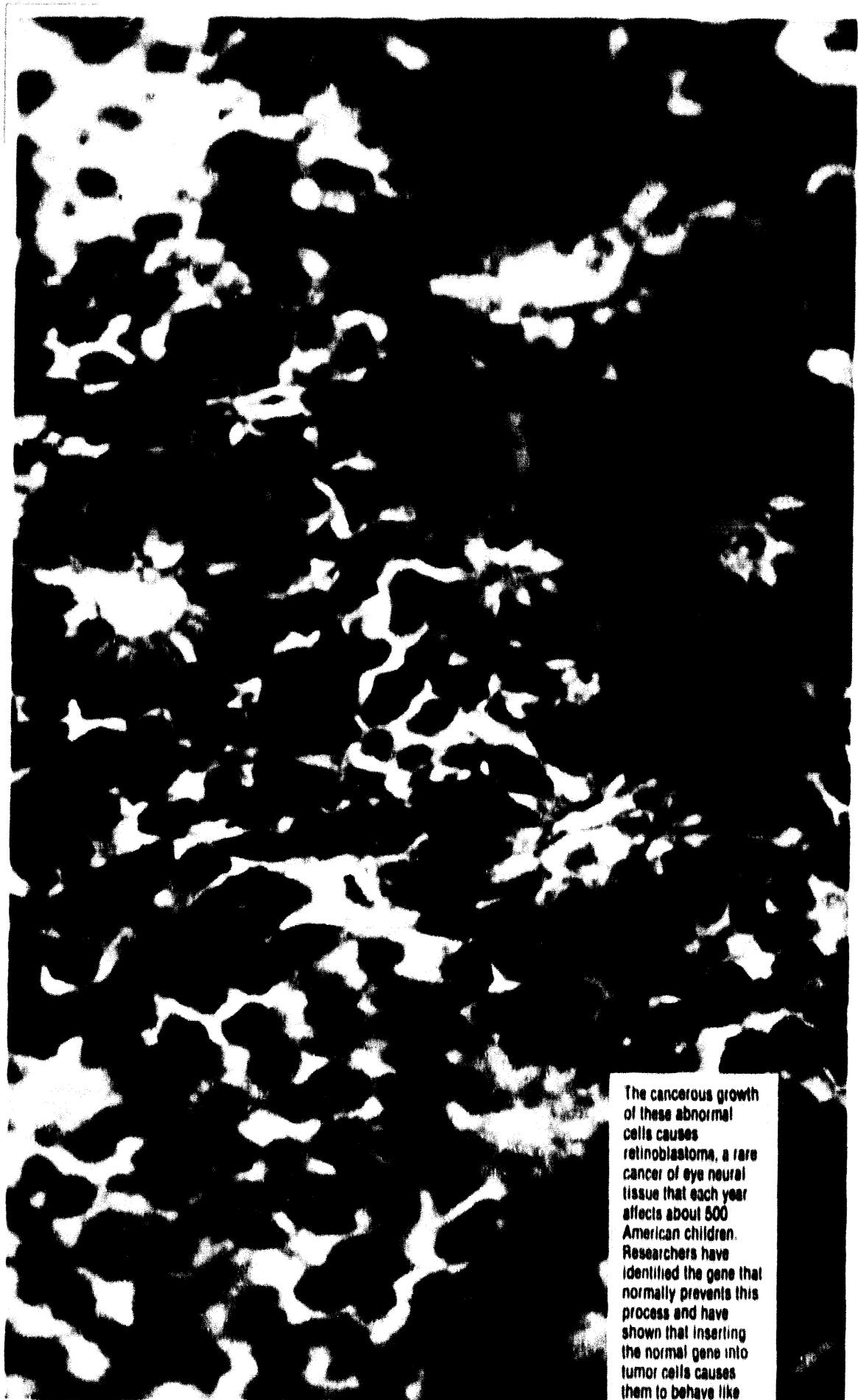


Improved imaging techniques such as CT, PET and MRI used to locate and diagnose brain disease and new surgical tools such as lasers have equipped neurosurgeons to perform operations not possible a short while ago.

stages of tumor development, from the premalignant to the highly invasive stages. The inherent relationship between brain tumor cells and normal cells limits the options for managing malignant brain tumors, and physicians often fear doing more damage than good through an attempt at extensive surgery. Tumor-killing doses of x-rays can severely damage normal brain components and the few, moderately effective compounds used for chemotherapy all have cumulative toxic effects on the body. Because of these limitations, extensive research needs to be directed toward determining the characteristics of a malignant brain tumor that set it apart from other tissues and which can then be used as the targets for therapeutic interventions.

Neurogenetic Disorders. Of all genetic disorders, one-fourth affect the brain and the nervous system of both young and old. Research in neurogenetics involves studies of genetically transmitted disorders of the brain and nervous system such as Huntington's disease, neurofibromatosis, tumors, dystonias, the hereditary ataxias and other diseases. Particularly devastating are childhood disorders such as Tay-Sachs disease, the leukodystrophies and Batten's disease, all of which inevitably lead to progressive brain deterioration, dementia and death. As a whole, these disorders currently affect more than 1 million people in the United States. Scientists hope to apply newly developed genetic techniques to the diagnosis and treatment of these diseases and other nervous system disorders not traditionally associated with genetic causes.

Within the last decade, scientists have identified the chromosomal location for several genes associated with disease in the nervous system, including those of Huntington's disease (chromosome 4), neurofibromatosis 1 (chromosome 17), von Hippel-Lindau disease (chromosome 3), tuberous sclerosis (chromosomes 9 and 11), Friedreich's ataxia (chromosome 9), idiopathic torsion dystonia (chromosome 9), Duchenne muscular dystrophy (X chromosome) and others. These studies have already led to presymptomatic and carrier detection in many disorders, and to the identification of the disease gene in others. The cloning of these genes will lead to more accurate testing and to the development of model systems in which to test novel treatments.



The cancerous growth of these abnormal cells causes retinoblastoma, a rare cancer of eye neural tissue that each year affects about 500 American children. Researchers have identified the gene that normally prevents this process and have shown that inserting the normal gene into tumor cells causes them to behave like normal cells, suggesting a potential therapy.

Communication and Sensory Disorders

Human senses include hearing, vision, tasting, smelling, touching, balancing and proprioception, although there is much overlap among the categories. They serve as the brain's channels of interaction with the world in which it operates. Most communication and sensory disorders are invisible and not fatal and, as a result, the attention given them in the past has been inadequate. Historically, many of these disorders have been inaccurately linked to mental illness or mental retardation. In the last decade, however, tremendous advances have been made both in understanding the disorders and in developing prevention and treatment interventions for them.

Understanding the organs and mechanisms of communication and sensation is vital for comprehension of the human brain. For example, the olfactory nerve is a route that allows substances, including chemicals and pathogenic organisms from the external world, to enter the brain directly, bypassing the blood-brain barrier. The eye, which has been aptly called the window of the brain, is the only location in the body where blood vessels can be directly observed and where certain vascular diseases mirror vascular diseases of the brain. The retina is the only clinically visible neural tissue in the body. Moreover, abnormal eye movements are also a common symptom of neurological disease.

■ Accomplishments

Vision. Seeing objects in detail, depth and color involves a series of highly complex processes. These include searching and scanning eye movements to localize an image on the retina; refining localization and achieving focus; and visual processing. The visual pathway consists of an intricate and well-defined set of connections. Disturbance of any part of this elaborate and precise system can lead to serious visual disorders.

Neuroscientists have identified specific regions of the brain involved in the perception of form, motion and color, which demands some of the most complex neural interactions occurring in the brain. Scientists using PET can view a three-dimensional map of activities such as color processing or motion processing in different brain regions of a human subject who is awake. MRI can be used to differentiate active brain regions from relatively inactive regions while a subject is involved in vision activities. Immunological studies have led to the development of monoclonal antibodies to locate specific transmitters in the retina and the brain and study how they function.

Knowledge of the neural circuits that control eye movements has increased rapidly in recent years. Location of the master circuit, the "neural integrator," has solved a longstanding puzzle of how the vast array of commands to the eyes controlled by a variety of systems are integrated in one discrete area. Scientists have classified five distinct types of eye movements. The vestibulo-ocular reflex (VOR) is driven by the organs of balance in the inner ear and helps to compensate for the motion of the head and body by keeping the target image stable on the retina. The VOR is a basic reflex that works in both darkness and light. Often the VOR is accompanied by a second class of eye movements used to center the eye in its orbit once the eye has reached the limits of its travel. A third type of eye movement is typically a voluntary fast eye movement used to acquire a target or object of interest. Another type of eye movement is used to follow slow-moving objects when the head is held stationary. The fifth type of eye movement allows us to keep an object stable on the retina as it moves either closer to us or further away. These eye movements do not work independently, but rather are combined during ordinary tasks. Understanding these very rich and complex interactions should provide fertile ground for further investigations.

Scientists recently localized the gene for a serious eye disorder, autosomal dominant retinitis pigmentosa, to chromosome 3. Retinitis pigmentosa is a family of inherited diseases, characterized by a progressive loss of vision due to the degeneration of photoreceptor cells in the retina of the eye. It is a major cause of blindness that affects more than 100,000 individuals in this country alone. Molecular genetic investigations in humans with retinitis pigmentosa and in animal mutants have revolutionized this entire field of research. Scientists studying patients with an autosomal dominant type of retinitis pigmentosa, for example, have recently identified a mutation in the gene for rhodopsin, a photoreceptor protein that is critical for night vision. In addition, scientists have begun to discover and characterize defective genes and proteins in a number of mouse and *Drosophila* retinal degeneration mutants.

Hearing. During the last decade significant progress has been made in understanding how hearing loss may be caused by environmental factors such as noise, drugs—including antibiotics—and toxins. Within the past year, scientists have identified the locations for the genes related to a number of important genetically transmitted forms of hearing impairment: one form of Alport's syndrome, albinism and Usher syndrome type 2, which is characterized by progressive hearing impairment, blindness and balance disorders. Gene locations have also been identified for neurofibromatosis type 1 and type 2, which produce tumors on the nerves, including the auditory nerve.

One-third of persons over 65 have a hearing loss sufficient to interfere with speech perception and effective communication, and the prevalence of such loss rises with increasing age. The inner ear is primarily affected, although changes in the auditory nerve and brain stem probably also contribute to the hearing disorders. Recent work has shown that with advancing age, certain neurotransmitters are depleted or reduced in some brain structures but not in others.

A new speech processor has been developed for use with multi-channel cochlear implants. Patients tested with the device show unprecedented speech perception accuracy, exceeding in some cases the results achieved with conventional hearing aids worn by persons with far less hearing loss.

Speech and Language. Studies of neuromotor control of speech indicate that stutterers have problems controlling and coordinating the many rapid sequential movements necessary for smooth speech production. The timing

and coordination of movements of the lips and jaw of stutterers have been found to be significantly different from those of normal speakers. Such findings suggest an underlying neuromotor control problem in stuttering, and have implications for treatment of the disorder.

Scientists have discovered that stroke-induced aphasia, characterized by an inability to speak or understand the spoken word, can be

improved by treatment with bromocriptine, a chemical that acts like the neurotransmitter dopamine. Furthermore, they have discovered that aphasia caused by stroke can be ameliorated by administering type I gangliosides immediately after the stroke.

Smell and Taste. Recent research on smell and taste has produced improved diagnoses of chemosensory dysfunction, data on significant causal factors and preliminary tests of possible therapies. Tests are being developed for the clinical diagnosis and categorization of chemosensory disorders.

Spatial Orientation. The sense of body position relative to space is derived through a variety of sensory systems that include vision, the organs of balance in the inner ear, and the tactile, joint and muscle stretch receptors. These signals converge in the central nervous system to produce an internal perception of body position. This multisensory integration of information is essential for normal posture, gait and eye movement. At least 75 million Americans will suffer from balance disturbances sometime in their lives. The brain, however, has a remarkable capacity to adapt to new sensory input and recalibrate sensory-motor relationships to re-establish normal movement function. Future research will be devoted to investigating how the brain reprograms its own software when faced with disease, injury or an unusual sensory environment, such as space.



The eye, sometimes called "the window on the brain," is the only body location where blood vessels can be directly observed and where certain vascular diseases mirror vascular diseases in the brain.

■ Future Plans and Potential Benefits

Currently, there is no cure for many retinal genetic diseases that progressively destroy the vision of people in all age groups. The Decade of the Brain will see new studies of genetic defects that can provide insights into the causes of retinal diseases, as well as the development of effective therapies to repair or replace defective genes that will aid in the cure of retinal genetic diseases.

Optic neuritis is the second most commonly acquired optic nerve disorder in people under the age of 50. Optic neuritis, which can

advance to nerve demyelination, is often found in patients who have or later develop multiple sclerosis. The goal of research in this area is to clarify the long-term course of changes in visual function in patients who have optic neuritis and multiple sclerosis. The research should also help explain the relationship between the two diseases.



Researchers from the National Institute on Deafness and Other Communication Disorders are mapping the gene that causes Waardenburg syndrome, one of the most common syndromic causes of hereditary deafness. In addition to hearing loss, Waardenburg syndrome is characterized by pigmentary changes, such as a white forelock of hair and, occasionally, one brown and one blue eye.

more about the functional specialization that exists at all levels of the visual system; 2) determination of the identities and actions of the neurotransmitters and neuromodulators in the visual system and how these substances are regulated and released; 3) development and testing of new mathematical models of eye movement systems; 4) analyses of the mechanisms of the vestibulo-ocular reflex; and 5) refinement of techniques for imaging the eye and the retinal nerve fiber layer, with the objective of measuring damage in individual patients and assessing clinical research results.

In the United States, approximately 2 million people lost their hearing before they acquired language (the pre-lingually deaf). A large portion of these individuals use a form of sign language as their primary mode of communication. Many use spoken English; many use both. The patterns of language acquisition in such individuals are little understood. We need to study patterns of acquisition of oral and signing language and their relation to cognitive and psychosocial development among deaf children. Factors associated with successful acquisition of oral language also need to be identified.

Identifying auditory dysfunctions within the central nervous system remains an art, particularly when unrelated inner ear dysfunction is

also present. A number of new diagnostic techniques under investigation, such as MRI and PET, may prove useful in this area.

Also necessary are multidisciplinary studies that focus on a number of specific hearing disorders about which little is known. Methods for early detection of acoustic tumors need to be refined. There is a need to better understand how infectious agents actually cause hearing loss, by finding the location of damage and determining how prenatal infection occurs. In addition, further research is needed to determine the incidence of severe hearing loss resulting from bacterial meningitis, and to document the natural history of the hearing loss once it has developed. The causes and mechanisms of specific language impairment are unknown.

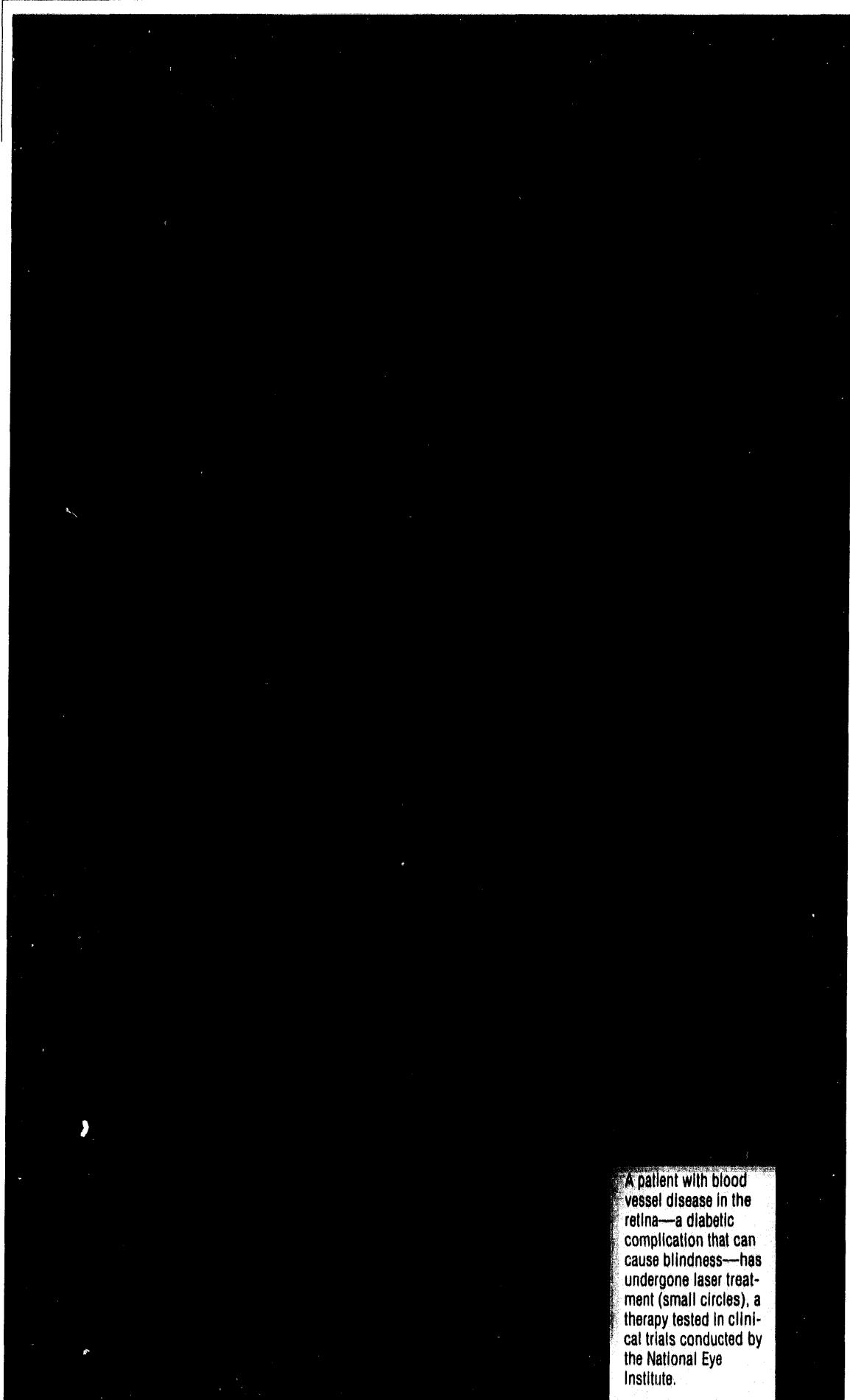
Auditory problems in children and the development and maturation of normal hearing are now appropriate subjects for systematic and comprehensive investigation. Research on embryonic mechanisms in the formation of the normal ear and also on normal, functioning auditory pathways in the brain will lead to an understanding of the mechanisms that produce congenital defects, and an ability to correct them. In addition, normal metabolic, biochemical and immunologic changes in the middle ear, the cochlea and the brain over the life cycle should be investigated. This research should be integrated with studies focused on characterizing the cellular basis of hearing and the mechanisms that regulate sensory cell regeneration and recovery of hearing in damaged auditory systems.

For patients who have extensive eighth nerve damage but are not candidates for cochlear implants, neural prostheses implanted in the central auditory nervous system may be a solution. Development and assessment of cochlear and neural prostheses should be continued.

Speech disorders occur with relative frequency following brain injury and in association with various neurological diseases. The dysarthrias, or speech execution disorders, occur in almost all diseases of the central nervous system, including Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease and multiple sclerosis. Research related to the underlying brain mechanisms, diagnosis and treatment of speech disorders is needed.

For the senses of taste and smell, research is needed to: 1) develop additional diagnostic methods for smell and taste disorders as well as instruments for monitoring their natural history; 2) investigate the role of the olfactory nerve in the transport of toxins and pathogens to the brain; and 3) find the causes of disorders of these senses and determine the prognosis for recovery. Since chemicals and pathogenic organisms can gain entrance to the central nervous system through the olfactory nerves, it is necessary to determine which of the viruses responsible for central nervous system infections travel this route and how to block this process.

Future research on spatial orientation should be directed toward the development of an artificial vestibular (balance) system. This vestibular "prosthesis" would aid patients with balance disorders that result from damage to the organs of balance in the inner ear or from central and



A patient with blood vessel disease in the retina—a diabetic complication that can cause blindness—has undergone laser treatment (small circles), a therapy tested in clinical trials conducted by the National Eye Institute.

peripheral neural damage. Since falling constitutes a significant health risk for the elderly, such a system could also aid elderly patients with balance problems. Eventually it could help astronauts during sensory adaptation to zero gravity and during the re-adaptation that occurs on return to Earth. A better understanding must be gained of how head, eye and limb movements are spatially directed in three-dimensional space. Most research to date has been restricted to movement in one plane of action to simplify the complexity of the problem. Expansion of our analysis in three dimensions will enhance our understanding of sensory-motor integration during natural body movements.

Relationship with the Environment. An estimated 25 percent of all compounds are neurotoxic, and about 44 percent of those produce substantial sensory system dysfunction. Physical agents such as noise or high-intensity light can also damage sensory organs. An extensive research program, focusing on visual and auditory function, is under way to examine the effects of chemical or physical agents on sensory function. The goals of this program are to develop procedures and strategies which can be used to prevent exposure, and to provide public education about compounds that are toxic to sensory systems. (See *Environmental Impacts on the Human Brain*.)

Computational Vision. A better understanding of human vision will enable scientists to design and implement machine-vision systems with sophisticated image-processing capabilities. Computational models of human vision with feature extraction and integration have been developed. By understanding and creating models of human vision, scientists hope to improve human interface with realistic simulators and to endow automated systems with biological visual capabilities. Much work remains to be done, however. Current research is aimed at improving and developing new models that account for visual processing that leads to the recognition of visual forms. A new conceptual system has recently emerged that explains the perceptual capability of humans to infer object qualities from incomplete or ambiguous visual information. The basic research developments emerging from this approach can be expected to have broad implications. Expected solutions to engineering problems in machine vision, visual person-machine interface design, and robotic control will find extensive industrial application. New visual prosthetic devices with the capability to serve as a "smart" visual processor for the visually impaired may also come from such research.

Much research on the sensory and communication systems has been pioneering work applicable to the whole human nervous system. Further research on the development, organization and function of the sensory and communication systems should have wide-ranging significance for understanding the principles of central nervous system and brain function that could illuminate the sources of various neurological and psychiatric diseases.



Dr. Francis Collins of the University of Michigan examines the leg of a young boy with neurofibromatosis, a genetic disease affecting many areas of the body, including the skin, nervous system and skeleton.

Development of the Human Brain

The human brain is the most complex organ system in nature. What is so remarkable is that the brain both coordinates major bodily functions and provides a capacity for self-awareness, for learning and for adapting to an ever-changing environment. The development of this marvelous machine is dependent upon processes that are set into motion at conception and result in a structure consisting of billions of cells.

When processes that guide the assembly and development of the brain go awry, the resulting physical and behavioral anomalies lead to disabilities—disabilities that cause enormous morbidity to the child and the family and, in the end, are the source of enormous costs to society. Epidemiologists estimate that in 2 to 3 percent of live births brain development is faulty, causing more than half of all human congenital abnormalities (including mental retardation). The cost of caring for developmental failure is more than \$20 billion per year in the United States. Therefore a complete understanding of the developmental mechanisms responsible for the function of the nervous system is essential; research in this area is critical for future prevention and treatment of these disorders.

Three examples—birth defects, growth failure and abnormal pubescence—serve to document the severity of the problem. Birth defects are now recognized as the major crippler and cause of death in infants, even as other causes of morbidity and mortality in this population gradually decrease. Of these developmental defects, malformations and abnormalities of the nervous system are among the most devastating. To address this critical health problem, research in the coming decade must focus on their etiology and prevention.

Each year, approximately 100,000 American children fall below the third percentile for height at school age. Aside from nutritional or genetic factors, a cause for this growth failure will be found in only about one-fifth of affected children, and only 1 percent will be diagnosed as having growth hormone deficiency. Because the brain is crucial for controlling normal growth and development, many of the unknown causes of growth failure will be found through detailed studies of brain function.

The metamorphosis of puberty and the psychological changes that accompany it have long intrigued scientists and clinicians, and there is a great need for more information about the brain-directed changes that occur during this stage of development. These changes provide drama enough when they occur normally at adolescence, but they are startling and disruptive in the extreme when they occur precociously in

toddlers or preschoolers. Less disruptive but equally exasperating to the affected individuals and their families is the delayed onset of puberty; adolescents with slowed physical and sexual development often experience daily rejections—rejections which may leave lasting emotional scars.

Abnormalities of sensory development also take a heavy toll on children's health. Approximately 3 percent of the population suffer from a loss of visual function in one eye (amblyopia, or "lazy eye"), a condition thought to result from crossed eyes, unequal visual input between the two eyes during very early postnatal development, or congenital cataracts during a critical period of development that extends from infancy through early childhood. Undetected, this condition can lead to permanent blindness that is otherwise totally preventable. Myopia, or nearsightedness, is a developmental disorder whose prevalence increases throughout childhood. Fewer than 2 percent of American 5-year-olds are myopic, yet more than 15 percent of high school graduates and 25 percent of the adult population are myopic. Both amblyopia and myopia are known to involve abnormal development of visual brain mechanisms.

■ Accomplishments

During the past 30 years, research on children has revolutionized our knowledge of cognitive, behavioral and psychological development during the period spanning birth through childhood. Infants are now known to be sentient beings who learn, remember, emote, perceive and meaningfully process sensory information within at least hours after birth. Scientists have identified cognitive capacities during infancy and characterized and followed their developmental milestones throughout childhood. The new knowledge gained about these factors, and the value of early stimulation on brain and cognitive development, formed the rationale for strategies for infants at risk and was the basis for social programs such as Head Start. Theories of cognition based upon developmental research have stimulated the growth of more powerful didactic methods for teaching our children and have informed us about the processes that may underlie thinking.

Technological developments in the care of newborns have improved their survival and neurologic health. The combined effect of the many scientific advances of the last 20 years has been a striking reduction in the mortality rate. Today more than 90 percent of infants weighing 1 to 1.5 kg at birth survive. Improvement in survival has been paralleled by improved neurological outcome. Most importantly, the proportion of very low birth weight infants surviving without handicap has increased from less than 10 percent to at least 60 percent. Nonetheless, a significant challenge remains.

Over the past 20 years, it has become clear that the central nervous system is vulnerable to dietary deficiencies. The dietary conditions that affect brain chemistry and function include chronic nutritional deficiencies, which often have lasting effects on the brain if they occur during development, as well as acute nutritional deficiencies, which produce short-lived neurochemical and behavioral effects. The greatest periods of vulnerability for the brain are late gestation and the early postnatal period. Reduced protein and calorie intake at this time pro-

duces deficits in glial cell proliferation and myelinization, and in the development of some nerve populations. Protein and calorie malnutrition also leads to neurotransmitter deficits that may exacerbate the enduring reductions in mental function observed in children who were severely malnourished early in postnatal life. Premature infants are a subgroup of special concern, because they are developmentally immature and must receive their nutrients from an artificial source by an atypical route. There are few biological data at present to guide appropriate nutritional strategy for ensuring optimal central nervous system development in premature infants.

In addition to food-related effects on brain chemistry and function, metabolic and other factors influence nutrient access to and utilization by the central nervous system. Studies on these factors range from gene regulation and enzyme expression to morphology, behavior and function.

Major technological breakthroughs in molecular biology and cell biology have occurred over the past 5 years, permitting identification of the processes that lead to neural tube defects such as spina bifida, meningomyelocele and anencephaly. These new approaches will permit the development of research strategies that will lead to appropriate interventions. The recommendations emanating from recent research conferences strongly suggest that a multidisciplinary approach is needed to identify the causes of neural tube defects.

A central question of developmental biology is how the nervous system is established in the embryo and how its complexity is generated. Using developmental models, scientists are now beginning to identify genes in mammals that are necessary for differentiation of nerve cells. The techniques of transgenic technology and homologous recombination provide powerful tools for identifying the function of developmentally regulated genes in mammals. Further, the availability of novel cell lineage tracers and image-processing techniques will allow developmental studies directed at characterizing the relationships between cell types and their patterns of interactions. This will permit scientists to identify the role of a cell's environment in determining what kind of nerve cell it will become and how these interactions will affect its function.

Additional scientific advances in human development include a staggering number of recent accomplishments that have direct relevance to brain disorders. These include intrauterine diagnosis and therapy, screening programs for various diseases such as PKU, genetic determinations, advances in the understanding of neuroendocrine control, identification of infants at risk for sudden infant death syndrome, and better understanding of the mental disorders of children. At the basic level, prodigious accomplishments have been made, especially in molecular biology and genetics, cellular biology, trophic factors, and understanding the development of synapses and receptors, as well as the action of neurotransmitters. These basic advances provide the fundamentals for the scientific accomplishments of the next decade of brain research.

Nobel Prize-winning research in the 1960s using animal models for amblyopia set the stage for our current understanding of how abnormal visual experience early in life can lead to profound changes in the "wiring pattern" and nerve cell activity of the brain's visual centers. These deficits can also be reversed during the critical period of development. Myopia in the growing eye can also be the result of abnormal visual experience during a critical period of development. Research in animals implicates the involvement of the dopamine system of the retina in this disorder. Further research on the anatomy, physiology and neurochemistry of these disorders will lead to more effective treatment and prevention strategies.

When partial or total hearing loss occurs early in life, the development of the structures in the brainstem that convey auditory information to the brain for comprehension and association may be inhibited. Scientists think that the effects of such central auditory changes on a child's ability to process auditory information and to develop speech and language skills are substantial. Even if the hearing loss can be cured, those central changes may persist. Recent preliminary studies suggest that the development of those central effects may not be inevitable, as had been widely assumed, but may be preventable or at least minimized. Application of low-amplitude patterned electrical stimulation to the cochlea has shown promise, as has the administration of a biological substance called a ganglioside. Thus, the treatment of children who suffer severe to profound hearing loss as a result of meningitis, trauma or other infections could be planned without the accompanying concern that delay in selecting a treatment would result in irreversible central auditory changes.

■ Future Plans and Potential Benefits

During the coming decade scientists will have a number of extraordinary research opportunities for identifying the processes involved in the development of the central nervous system and its behavioral capacities. At the basic biological level these processes include the molecular and cellular bases of neuronal specification, the establishment of appropriate connections among neurons, and the association of neurons into functional anatomical units. At the basic psychobiological level these include the mechanisms that integrate cognition, memory, learning and language acquisition. An understanding of these underlying processes is the critical first step toward the development of appropriate intervention strategies for the heterogeneous disorders of development.

One of the major areas of excitement is in neurogenetics. Enormous progress has been made with a few disorders such as Gaucher's disease and muscular dystrophy. However, new research strategies are needed to locate genes related to the specific nature of the metabolic defects. (See *Basic Research*.)

The development of treatment modalities for neurogenetic disorders is especially difficult, because of challenges posed by the nervous system that are not present in other organ systems. Neurons, for example, are non-dividing cells, making it harder to introduce genes. The complexity of the brain creates targeted delivery problems, and the blood-brain barrier prevents many drugs and biological agents from entering the



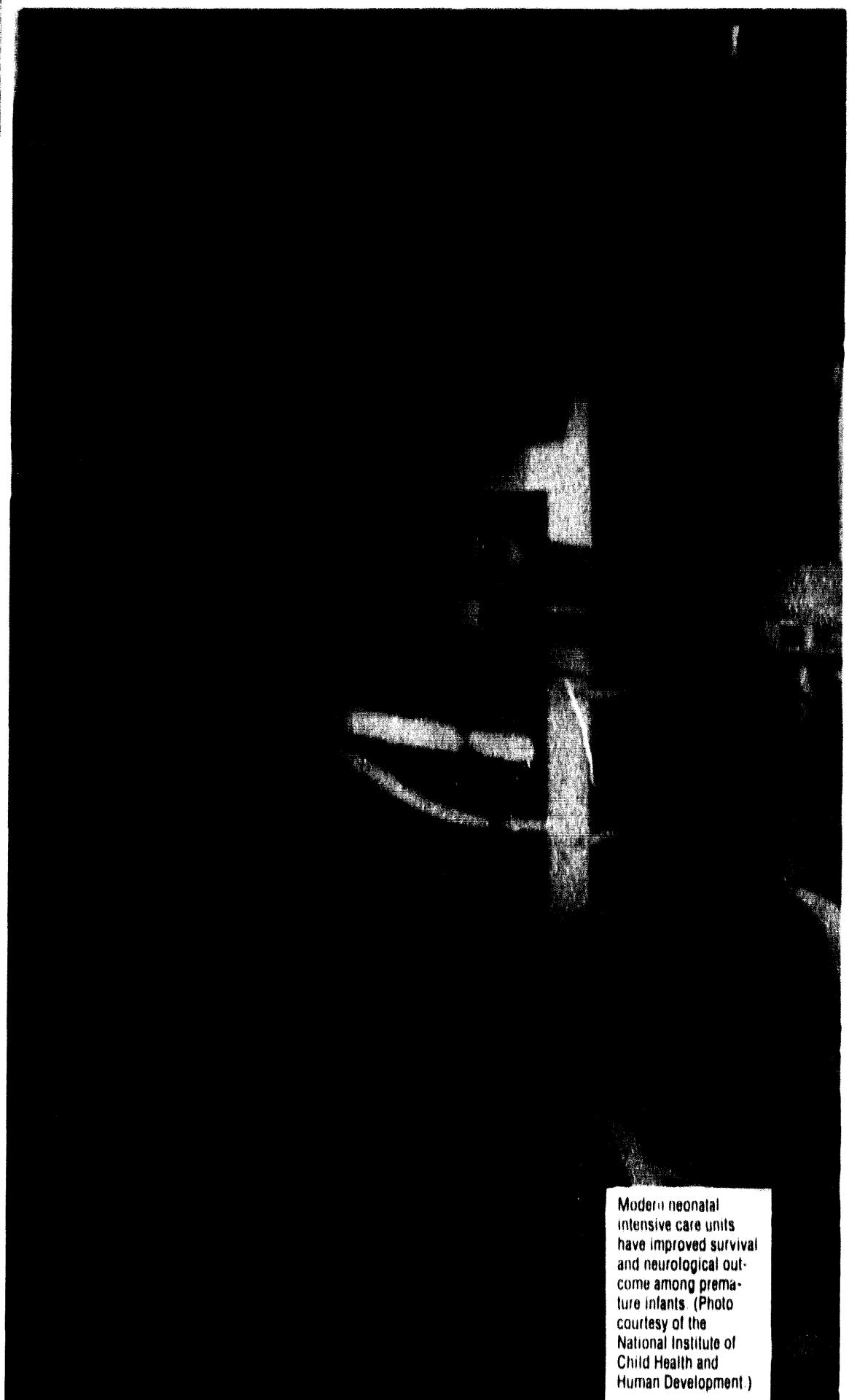
brain. Nevertheless, a number of promising new strategies are on the horizon: viral vectors may allow gene delivery to the nervous system, production of genetically altered cell lines may offer means for brain repair by autologous brain cell transplantation, bone marrow transplants may correct some enzyme deficiencies, and osmotic perturbations—as well as chemical carriers—may provide means for traversing the blood-brain barrier. Scientists participating in the Human Genome Project will be identifying the genes for a number of genetic disorders of the developing nervous system, such as Tay-Sachs disease and Rett syndrome.

Research on the developmental effects of abused drugs is a top priority, involving major methodological issues related to studying the effects of prenatal drug exposure. Research in this area includes developing animal models for studying the neurobiological and neurobehavioral effects of drug exposure during development, human clinical studies, epidemiological studies of behavioral and psychosocial development, and treatment and prevention studies. Developmental neurobiology studies address the need for precise, systematic information on the existence, persistence and functional significance of brain effects due to perinatal exposure to drugs of abuse.

In developmental psychobiology, future questions will focus on the general issue of when and how relationships between the brain and behavior develop, especially the timing of human acquisition of the capacities to know and become aware, to learn and remember, and to communicate through speech, language, reading and writing.

Behavioral scientists have begun to employ new technologies to characterize electrophysiological events associated with the development of cognition (event-related potentials, PET scans and BEAM) in young infants. Classical conditioning techniques involving the eyeblink reflex are being studied not only in animal models but even in human babies to gain an understanding of the role played by the hippocampus in

Recent research in children has revolutionized knowledge about cognitive, behavioral and psychological development



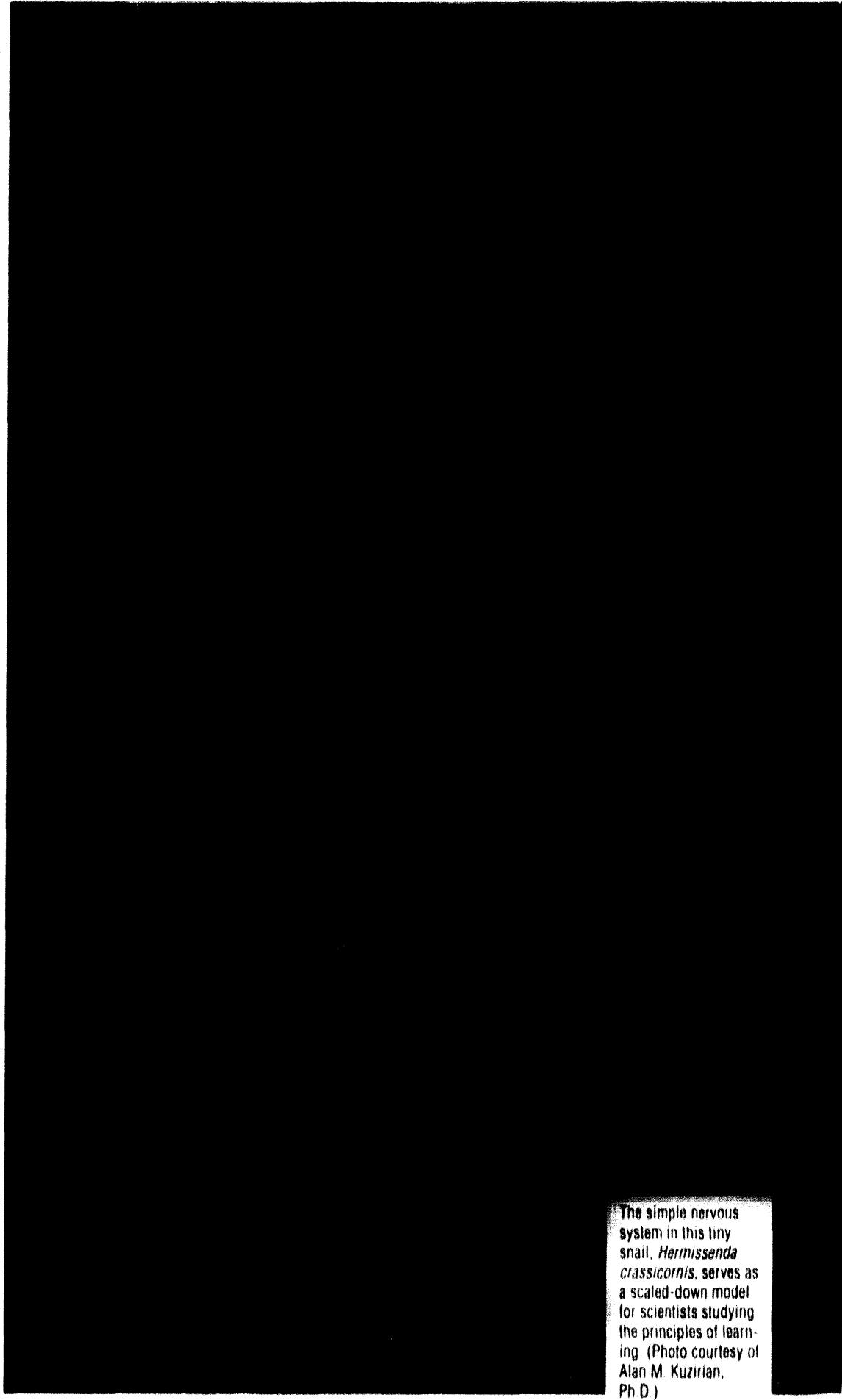
Modern neonatal intensive care units have improved survival and neurological outcome among premature infants. (Photo courtesy of the National Institute of Child Health and Human Development.)

information processing associated with memory development. Comparative studies are under way using primate models to help gain an understanding of the evolution and development of language learning. Studies using animal models are now providing the first information concerning the capacity of developing fetuses to learn. Studies using animal models are now providing the first information concerning the capacity of developing fetuses to learn *in utero*. Such experimental work will supplement a growing body of information—collected via ultrasonography—on behavioral patterns typical of the developing human fetus. Studies of adolescents are under way to determine how lateralization of brain function develops and comes to subsume different types of intellectual capacity—such as mathematical and verbal abilities—in boys and girls.

Non-human primate models will be employed to study genetic and environmental effects on the expression of individual differences in response to mild environmental exposure and stress throughout development. Such differences are monitored in a variety of systems reflecting multiple levels of analysis, including measures of hypothalamic-pituitary-adrenal activity, psychophysiological reactivity, levels of monoamines and their metabolites in the cerebrospinal fluid, and complex behavioral repertoires.

An understanding of maternal-fetal interactions and early childhood development will be critical to identifying what causes developmental delay, how environmental agents affect low birth weight infants, and how pediatric AIDS and maternal substance abuse affect the neurobehavioral development of the child. As science becomes more sophisticated, multidisciplinary studies will be necessary for identifying the complex etiologies of such developmental disorders as spina bifida and hydrocephaly, mental retardation, and learning disabilities such as dyslexia.

Results from the planned research outlined above will shed light on the causes of developmental disorders of the nervous system and provide the basis for designing appropriate prevention and intervention strategies.



The simple nervous system in this tiny snail, *Hermissenda crassicornis*, serves as a scaled-down model for scientists studying the principles of learning. (Photo courtesy of Alan M. Kuzirian, Ph.D.)

Learning and Memory

Perhaps the most critical function of the nervous system is to learn and retain information. This area of research concerns the study of intelligent systems that see, hear, understand and produce speech, remember, solve problems, make decisions, prove theorems, and design innovative products. It is an inherently interdisciplinary activity, embracing cognitive psychology, linguistics and artificial intelligence, but increasingly involving neuroscience, engineering, other behavioral sciences and social sciences as well. This rapidly maturing scientific effort is distinguished by its use of rigorous mathematical and computer-simulation models to characterize the properties of intelligent behaviors, both biological and artificial.

The appeal of research on learning is first and foremost the promise of understanding the workings of the human intellect, one of the most ancient and recalcitrant puzzles known. The extent to which human intelligence is similar to and different from artificially intelligent systems has been a recurring scientific question since the invention of the first crude computers. But there is important economic potential in these studies as well. Useful, large-scale computer models and engineering devices that exhibit intelligent behavior continue to be tantalizingly out of reach. The nation needs to realize the potential economic gains inherent in the commercially viable, artificially intelligent computer systems that result from this research. In this regard, fundamental brain research directed toward understanding learning and memory will provide important information for medical, behavioral and technological applications.

■ Accomplishments

Concepts of how neurons function in learning have changed in recent years. Modern research is close to thoroughly understanding some fundamental features of the molecular basis of memory, learning and the "plasticity" of behavior. Investigators are achieving insights into how simple nerve systems adapt and how neurons that form local circuits proliferate. Scientists now know that long-term memory involves actual structural changes in the brain, and that short-term and long-term memory involve different areas and processes in the brain. One line of research involves the search for the substances that change in concentration or distribution in the course of learning. These substances include various neurotransmitters, "second messengers," ion channels and receptors. One group of molecules in the brain—known as excitatory amino acid receptors—are used by nerve cells to communicate in diverse brain functions such as memory, learning and cognition. The malfunction of these receptors may lead to learning, memory and other neurological disorders.

Brain development during infancy and childhood affects learning, memory and cognition in important ways. Very low birth weight, preterm infants have been found to be at risk for mental retardation, developmental disabilities and a variety of learning disorders.

Stimulation of growing infants and children significantly affects the way their brains develop. In order to provide optimum stimulation and development, it is important to understand how stimulation "couples" with the developmental process.

Early nutrition also has been shown to have a significant effect on brain growth, early development and later cognitive development. Children who ingested a deficient formula at an average age of 7 months of age, a time when the brain is undergoing rapid growth, demonstrated at ages 2 and 4 a correlation between the length of time they received the deficient formula and low IQ scores. At 9 and 10 years of age these children showed several functional deficiencies in speech and language tests when compared with a group of age-matched controls.

Several areas of research are receiving special attention. Studies to measure brain electrical activity hold great promise for further progress in diagnosing areas of brain dysfunction. For instance, among children with reading disorders, measurements of brain electrical activity vary according to the type of reading disability they have. This analysis also enables objective discrimination between normal and learning-disabled children. Because learning disabilities result from brain dysfunction, increased understanding of the basic mechanisms by which brain cells store and transmit information is crucial. For example, investigators are examining the relationship between the brain's neurochemistry and attentional deficits in learning disabilities. These studies are revealing the biological basis of fundamental brain dysfunction, and should provide the opportunity for more effective therapies. A new frontier in the field of learning disabilities research is provided by brain imaging technologies like PET and MRI. These tools provide insights into the brain networks involved in performing functions such as reading and calculating. They also can relate brain function and structure to specific learning disabilities.

As part of research on the neurological basis of language and learning, adult dyslexics who had profound reading disabilities in childhood were compared with control subjects on a speech-discrimination task while undergoing PET. Significant differences between the two groups suggest that language- or reading-impaired individuals have an inability to use, or inefficiently use, those areas in the left temporal lobe that most people use to process speech and language. To compensate, corresponding regions in the right hemisphere temporal lobe are engaged in speech processing, albeit with less efficiency. Scientists are currently analyzing other areas of the brain that may be used for speech processing.

Significant research is directed toward understanding the fundamental information-processing characteristics of humans, the nature of acquired skill and knowledge, the processes of learning such skills, and the instructional strategies to foster such learning. Four specific goals are: 1) to define human "cognitive architectures," i.e., the information

coding system, the neural processes that operate on that information, and the mechanisms that control those processes to accomplish learning; 2) to provide precise descriptions of knowledge and skill in terms of the cognitive structures and processes that generate the desired performance; 3) to develop a theory of complex learning that explains the processes by which structures of knowledge and complex cognitive processes are acquired, and how they develop from less complex knowledge and skill; and 4) to provide a theory of instruction that specifies how to deliberately foster and optimize learning processes with sufficient precision so that artificially intelligent tutoring systems might be developed to provide effective instruction. The impact of such research efforts on new and more powerful strategies for education could be dramatic and very significant. Optimal teaching strategies can be achieved only if we understand how to optimize conditions vis à vis how the brain acquires, stores and retrieves information.

In studies such as these the technical approaches taken are quite diverse, corresponding to the diverse research questions associated with the four program objectives. Formal computer models have been developed that explain the basis of the differences between different ability levels in tests of spatial ability, general reasoning and mechanical reasoning. Neural evidence can be used to answer questions about the learning process to predict performance during successive stages of learning. One principal objective of this research is to use neural evidence to provide a better description of fundamental capacities of humans to process information.

■ Future Plans and Potential Benefits

During the Decade of the Brain, considerable progress will be made in understanding how the brain stores memories and how we use this knowledge to interact successfully with our environment.

Research in cognition is being encouraged in areas ranging from mathematical schemes dealing with simple organisms to clinical studies of patients with neurological disorders. Some of the investigations envisioned could include the following:

- Investigation of the locations of learning and memory functions through the use of brain scanning devices.
- Research on non-human primates engaged in language-relevant communication, including the use of numbers, and in repetitive, event-related activities.
- Interdisciplinary approaches that bring together scientists to investigate fundamental issues in learning and memory, ranging from the genetic and molecular to the behavioral.
- Comprehensive analysis of gender differences in the effects of neurological injuries upon standardized cognitive measures, with attention to comparing patients with differing locations of injury, right- or left-handedness, etc.

Learning and memory have long been suspected of being especially vulnerable to toxic substances found in the environment. In the future, investigators will focus on better understanding the relationships between environmental chemicals and the areas of the brain related to cognition, learning and memory. Human research will be complemented by animal research to better define the sites in the nervous system vulnerable to attack by neurotoxic chemicals and the mechanisms by which environmental chemicals adversely affect learning and memory. For example, there is currently great concern regarding the extent to which Alzheimer's disease is associated with exposure to aluminum, and the extent to which chronic exposure to organic solvents is related to the dementia that accompanies "painters' syndrome." Additional research is needed to pursue these important questions.

It is difficult to make sweeping generalizations about how a nutritional deficiency will affect any one individual because cognitive development is dependent on genetic as well as environmental factors, and because the relationship of the individual to the environment is interactive. Studying populations that experience similar deficiencies, however, may give us clues as to how the brain reacts to adverse nutritional conditions.



Theories of cognition based upon developmental research have stimulated the use of more powerful methods for teaching children and have led to a more profound understanding of the processes that underlie thinking.

The effects of manipulations of the amygdala, a brain structure located deep within the cerebral hemisphere, on learning and the processing of sensory information will be assessed. One planned study will investigate whether the amygdala

contributes to the establishment of an increased state of arousal in the presence of stimuli. The results should yield new and important information concerning the brain circuits that contribute to the processing of sensory information and the most optimal conditions for learning.

It is known that the brain structure called the hippocampus is involved in many forms of learning. One study is investigating a novel theory that the hippocampal formation enables an animal to construct a single representation of the joint occurrence of two or more stimulus elements. An important point of this theory is that it provides a possible explanation of how animals can solve problems in parallel to arrive at non-linear solutions. The hippocampus also has a large number of receptors that detect the presence of stress-related hormones in the blood. Investigators are attempting to determine how stress negatively influences learning and memory, and how the presence of stress hormones affects the normal function of the hippocampus.

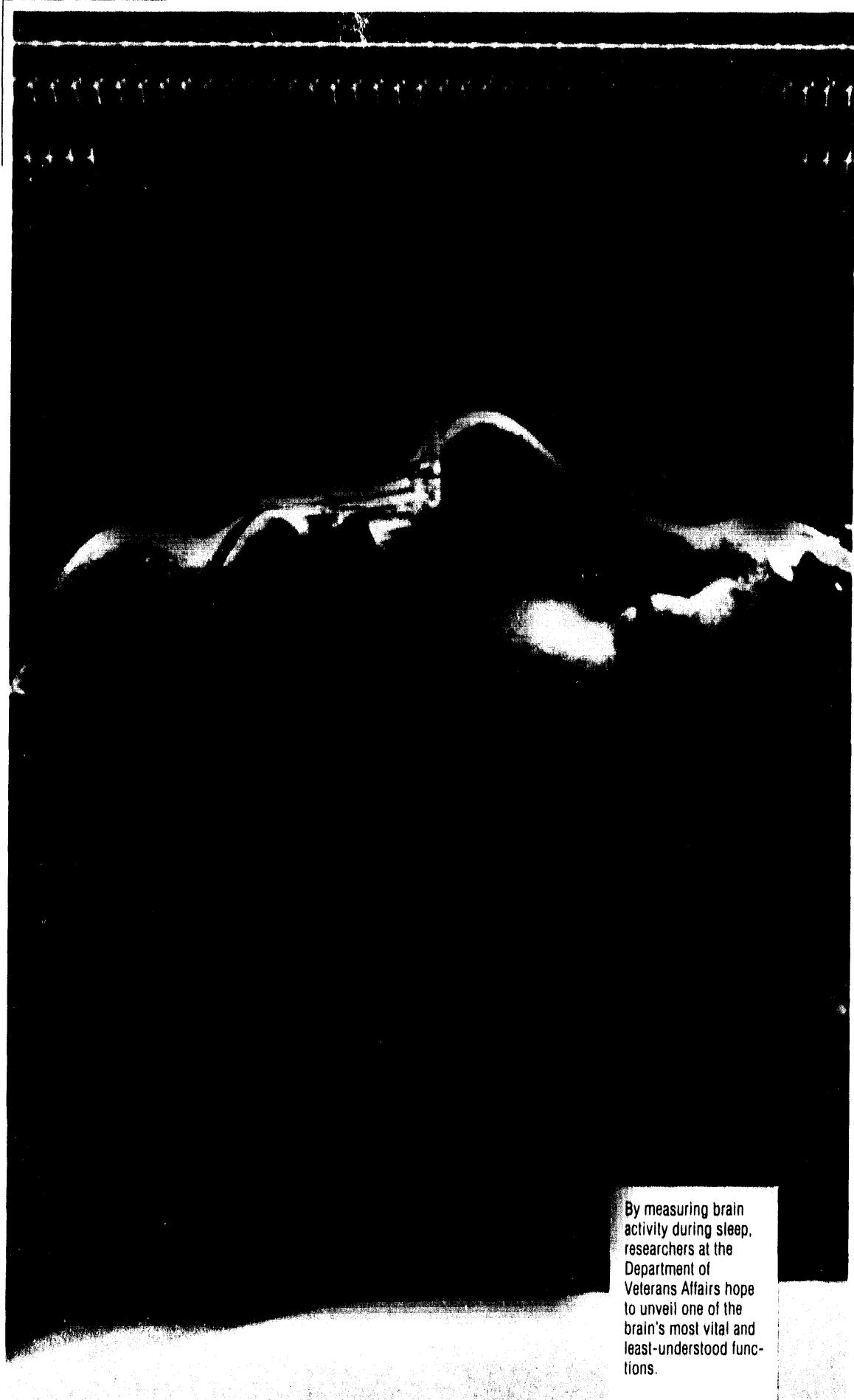
As discussed in detail in *Drugs and the Brain/Addiction*, the brain is a major target for the actions of alcohol and other drugs of abuse. The alterations in brain learning and memory functions due to alcohol and other drugs of abuse are an important focus for research. Studies of learning and memory can add to our understanding of drug abuse by

clarifying the role of learning (conditioning) in the addictive process. Such studies are important for understanding drug tolerance, sensitization and perhaps craving. Since there is a growing public concern that drug abuse in the workplace impairs cognitive processes and performance, studies are needed to characterize the acute effects of drugs on cognition and performance and to evaluate potential residual effects. Residual effects may occur during drug withdrawal, or might be long-lasting or irreversible changes of drug-induced neurotoxicity. Opiate-like substances which are naturally occurring in the human nervous system modulate learning and memory, and studies of these effects may improve our understanding of opiate addiction and the physiological role of these substances related to cognition. During the Decade of the Brain, research will clarify the influence of drugs of abuse on the neural areas involved in the processing, registry and retrieval of sensory information as well as on arousal and motivational/attentional factors that modify learning, memory and performance. The short-term and long-term consequences of drug abuse on learning and memory processes will be examined.

In neurolinguistics and neurobiology a number of advances can be expected. Scientists hope for an improved understanding of the regions of the brain implicated in developmental dyslexia, attention deficit disorder, language or reading impairment, autism and other diagnostic categories that have some relationship to learning disabilities.

Despite the research advances of the last 20 years and the increased availability of services, a majority of hearing-impaired children still fail to achieve functional literacy. Severe to profound deafness in early childhood has been found to adversely affect subsequent achievement in reading and writing. The severity of the problem suggests that this issue needs careful attention. Research on the reading and writing abilities and deficits of those with severe to profound deafness is being encouraged.

Additional planned research includes studies of how the expression of certain genes may be affected by neuronal activity during learning. Of particular interest are genes related to the elements responsible for communication between neurons (synapses). Construction of specific neuronal circuits may be possible with further development of nerve cell culture techniques. Modern techniques may enable the study of the connections, coding capabilities and development of complex, functioning assemblies of neurons. In particular, it should be possible to test how such complex, but well defined, nerve systems react to activation and chemical agents. Having reliable structural information, as well as cell lines that have high levels of receptors involved in learning, should enable neuropharmacologists to design and test new drugs to treat several neurological and learning disorders.



By measuring brain activity during sleep, researchers at the Department of Veterans Affairs hope to unveil one of the brain's most vital and least-understood functions.

Rehabilitation and Restoration of Function

Although more people today survive injuries and illnesses of the brain and nervous system, there are significant gaps in the knowledge and application of rehabilitative techniques that will help restore cognition, communication, sensation, movement control and mobility for these victims. Rehabilitation efforts have focused on developing and evaluating effective and affordable systems of rehabilitation, adaptable housing, assistive devices and programs to serve the needs of people with disabilities. These efforts include research on head and spinal cord injury, support for rehabilitation centers and universities conducting rehabilitation research, training of health professionals to implement model techniques of rehabilitative care, and development of programs to reduce disabilities. Infants and children born with sensorimotor deficits have different handicaps from those who lose functions later in life, and therefore their rehabilitation needs are different.

■ Accomplishments

Brain and Spinal Cord Injury. Traumatic brain injury is the leading cause of disability in children and young adults, affecting 400,000 to 600,000 people annually. Every 7 minutes someone becomes permanently disabled as a result of a head injury. In addition, each year 10,000 to 12,000 Americans are disabled by trauma to the spinal cord. The cost of care and services for patients with traumatic brain injury alone approaches \$25 billion per year. A major advance in research on injuries to the central nervous system is the discovery that there is a period of time immediately after the injury during which neurons surrounding the lesion are sick, but still alive. Intensive effort is being directed toward discovering the best approaches for salvaging those vulnerable neurons. Scientists now have substantial evidence that if the patient's brain or spinal cord is treated within 8 hours of injury, permanent damage can be prevented.

Prostheses. Federally conducted and supported research and development have produced internationally acclaimed accomplishments in comprehensive rehabilitation. The development of *artificial limbs* is one area of noted accomplishment. The foundations laid during the period after World War II have made American-developed techniques for casting, fitting and aligning artificial limbs the standard, not only in this country, but throughout most of the world. More recent rehabilitation research has led to such accomplishments as an improved artificial knee, a myoelectric elbow and interchangeable electric hook and hand, and the hydraulic ankle. Prostheses need to be developed for the special needs of the growing child. Currently, researchers are studying the use of robotics to assist those with spinal cord injuries. Researchers are developing a robotic arm that responds to voice com-

mands, permitting a paralyzed individual to engage in such activities of daily living as personal grooming, brushing teeth, washing and eating.

Pioneering efforts and accomplishments are emerging from *neural prostheses* programs. A neural prosthesis is a rehabilitative device which interfaces directly with the nervous system to replace or extend function in neurologically disabled individuals. Research includes studies in stimulation of the human nervous system, neural transplantation and implantable microstimulators for muscle stimulation. Other efforts focus on developing auditory prostheses for the deaf, bladder control prostheses for spinal cord injury victims, neuromuscular stimulation for paralyzed individuals and visual prostheses for the blind. Some of these devices will be helpful for the 11,000 children born every year with spina bifida, the major cause of mobility impairment in young children.

Neural prostheses require very small electrodes that interface with nerve cells, creating significant technical requirements. Considerable effort is being placed on improving electrode materials and developing new, biologically compatible materials so that electrode function can be further improved. Studies using animals to determine safe levels of electrical stimulation are also in progress.

The first electrical recordings from the human brain using microelectrodes that contain integrated electronic amplifiers were made in 1989. Recordings of brain activity using electrodes such as these offer the promise of providing a reliable system for generating commands to control prosthetic muscle stimulators in paralyzed individuals. A new electrode implanted through the skin and designed for stimulation of paralyzed muscle has been studied. Eighty percent of these electrodes remain functional after 1 year of implantation. A quadriplegic individual who received the first implanted neuromuscular stimulation system has had the implant a total of 3 years and has had no significant complications.

There is a great need to determine the most effective techniques for remediating the neurobehavioral effects of traumatic brain injury.

Hearing. Sensorineural (nerve) and mixed conductive hearing loss are currently treated with hearing aids. All of these aids have inherent problems, some of which should be alleviated by implantable hearing aids that are capable of directly driving the middle ear bones (ossicles). One significant breakthrough is the development of a completely digital (computerized) hearing aid. Also, a new speech processor has been developed for use with ear implants. Patients tested with the device show unprecedented accuracy in speech perception.

The precursors of regenerated sensory cells may be the key to the self-healing of the ear's sensory tissue, just as the cells that produce new skin are the key to wound healing. The precursors of animal sensory cells have been identified and are the focus of intense investigations to evaluate the molecular mechanisms, as well as treatments that may be used to trigger and to control the healing process.

Vision. Research on low-vision impairments is aimed at enhancing remaining vision, evaluating new and existing optical aids, developing

video magnification or image-enhancement systems, and discovering other ways to improve visual capabilities and performance. Researchers are also studying whether different combinations of color contrast and luminance enhance or diminish visual performance. Others are designing a prototype "intelligent" magnifier on a computer that will have a high-resolution scanner to locate an image and adjust its magnification. A small, portable reading aid that carries an image via optical fibers from the printed page to a hand-held microscope eyepiece enlarges the image and provides a large field of vision and good resolution of individual letters.

Restitution of Function. Scientists have explored a variety of approaches relating to restoring nerve function. These include tissue implants to replace damaged nerve cells and the application of agents designed to stimulate regrowth and repair of injured nerves. It is likely that in some instances both approaches are effective and the implant itself may stimulate nerve regrowth.

New research results have shown that very high doses of the steroid methylprednisolone given promptly to patients with spinal cord injury show significantly reduced loss of sensation and motor function. This has rapidly established a new standard of treatment for both neurologically complete and incomplete spinal cord injuries. Further investigations will evaluate the efficacy of nonsteroidal, rationally designed drugs and attempt to determine if even earlier treatment holds greater promise.

It is particularly important to study and understand how the brain reorganizes itself during rehabilitation after injuries to one or both hemispheres. There is also a great need to design patient-specific strategies for rehabilitation that will enhance the efficiency of current motor, language and cognitive retraining after stroke or head trauma.

Research on recovery after stroke and head injury reveals that the brain is functionally more dynamic than was previously believed. Neurons may be recruited from active areas of the brain to perform alternate functions. Recent research on injury and regeneration in the nervous system has led to optimism that injured neurons can survive and that regrowth is possible. However, basic questions still need to be answered. For example, it is not known when neuronal cell death is complete, how long the injured axons can sustain regeneration, whether support cells retain their normal characteristics, and if blood supply returns to normal after injury. This work has important implications in the restitution of function of patients with motor deficits following a stroke or other type of brain injury. (See *Brain and Spinal Cord Damage*.)

Investigators are examining the effects of electrical fields on recovery of function after acute contusion injuries of the spinal cord. Nerve growth and neurotrophic factors represent another possible avenue to regrowth and regeneration, and the discovery of such factors in recent years has generated considerable interest.

Addiction. Advances have been made in research on rehabilitation for those with addictive disorders. Scientists have developed medications

that reduce the craving for nicotine, block the effects of heroin, and reduce withdrawal effects from drug dependence. (See *Drugs and the Brain/Addiction*.)

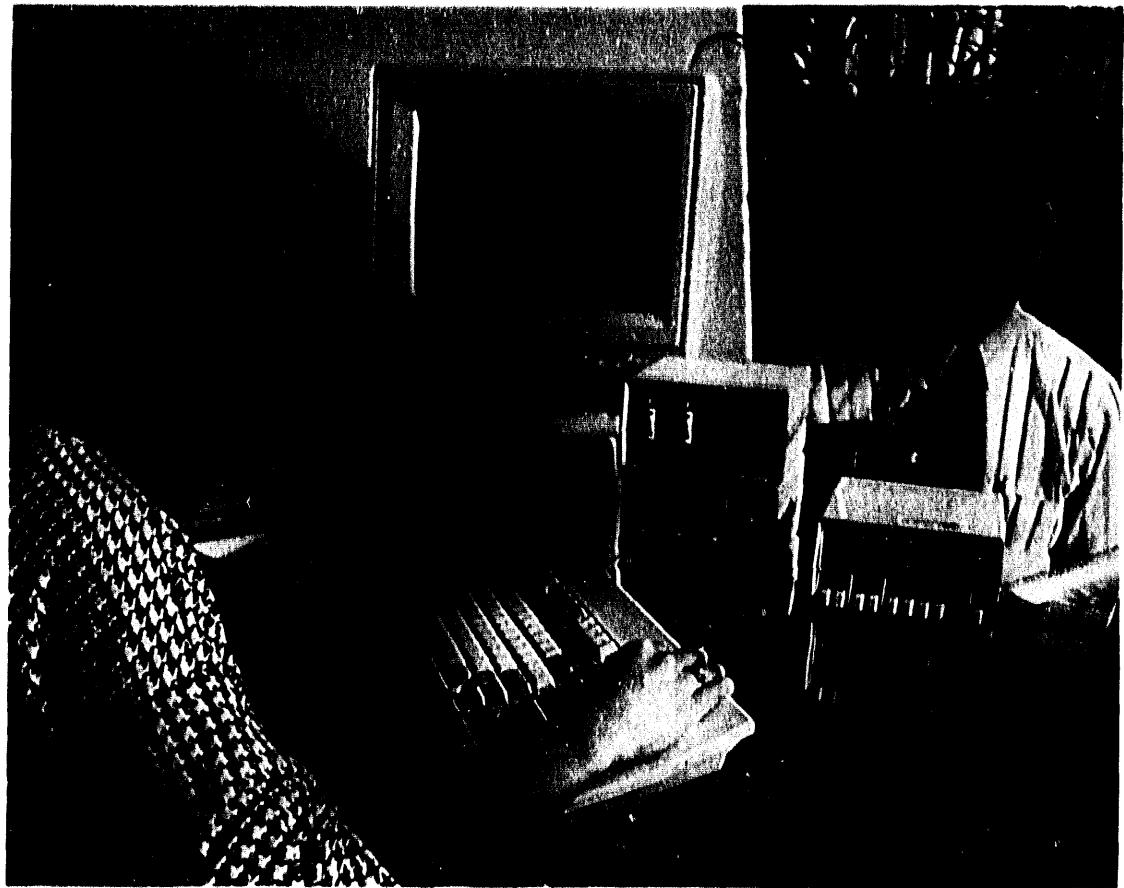
Imaging Technology. Investigators are conducting a number of innovative research projects on new imaging technology that may assist in the rehabilitation of nervous system damage. One example of this is the use of MRI in patients with head injuries. Brain lesions that would have gone undetected are now being found using MRI, resulting in a need for rehabilitation in patients who otherwise would not receive such care. Improvements in the speed of MRI scanning and in computer software that detects and draws portions of the brain are providing a new level of refinement to the study of brain volume, shape and form differences in children with severe reading disability (dyslexia).

Studies of language disabilities and language distribution using PET are identifying active areas of the brain in an effort to guide and evaluate rehabilitation strategies. PET studies of the phases of paralysis have been used to develop new approaches for clinical management.

Studies using PET are also beginning to detect differential brain metabolism in children and adults with attention deficit disorders. In addition, PET technology has provided a means of analyzing brain metabolism in children and adults with dyslexia.

Early detection of metabolic differences in children with attention deficit disorder and/or learning disabilities may permit differential treatment interventions. The information gained from such studies can aid in the design of specifically tailored programs that will maximize remaining functional capability of the nervous system.

Measuring the electrical activity of muscles near the temples, which can tighten during anxiety, is a first step toward biofeedback therapy aimed at relieving tension in patients with post-traumatic stress disorder.



■ Future Plans and Potential Benefits

New and developing areas of research on rehabilitation and restoration of function are:

- The study of factors that promote the survival and growth of neurons, and the study of supportive nervous tissue and its interaction with neurons.
- Identification of the genes that control the growth state of neurons.
- Investigation of how severed or damaged neurons reconnect with target cells.
- Refinement of long-lived electrodes for use in neural prostheses that can safely stimulate the nervous system.
- Investigation of the insertion of cultured neurons, grown on an electrode probe, into the central nervous system.
- Development of simple, quick and cost-effective tests to assess the specific visual components of various tasks, in order to provide a comprehensive picture of a patient's visual capacities.
- Determination of the features of an object that are required for its recognition to assist computational vision researchers in developing low-vision aids.
- Support for new low-vision aids to assist with drop-off detection, e.g., curbs, ramps and stairs; image processing; route finding; and text navigation.

Implantation of tissues, cells and cellular products into the central nervous system continues to offer promise for rehabilitation after spinal cord injury. Components of the nervous system and of placental tissue appear to foster the growth of nerve fibers. One possible new area of potential treatment for central nervous system trauma is the use of nervous tissue from fetal animals to replace damaged areas of the adult brain or spinal cord. Work is needed to understand the interactions between the host nervous system and the implanted tissue, to examine the long-term survival and growth of the implants, and to assess the potential of the grafts to restore lost function. Studies on neural tissue growth after implantation into brain and spinal cord are continuing, as are studies of the effect of growth factors on regeneration and repair. Efforts will be made to prolong the survival of cell grafts.

The results of research using animal models suggest that common neurobiological mechanisms may underlie alcohol, nicotine and psychoactive drug addiction. Future research is needed to understand the relationships of the neurophysiology of drug addiction and alcohol dependency, and to identify the rehabilitative efforts that may address



This is one of several patients involved in a multicenter trial that recently demonstrated a dramatic reduction of neurological damage when very high doses of methylprednisolone are given within 8 hours of spinal cord injury (Photo courtesy of Lloyd S. Jones.)

the needs of patients with addictive disorders. Essential to the rehabilitation of the patient addicted to alcohol or other drugs is the development of pharmacological agents that directly interfere with drug-taking behavior.

Great uncertainties exist in our understanding of how the nervous system compensates for exposure to environmental chemicals.

Research is needed to better understand how conditions of exposure affect the rate and extent of functional compensation, the cellular and molecular mechanisms involved, and whether there is residual risk following compensation.

The underlying processes involved in the recovery of damaged neurons must be understood to develop rational schemes for rehabilitation after injury to the optic nerve network. Related research problems include the reduction of cell damage, the stimulation of appropriate nerve growth, and the promotion of selective connections between nerve cells. Factors outside the neuron may determine the success or failure of nerve regeneration. Study of these complex cellular interactions requires multidisciplinary work.

For some speech-impaired individuals, the ability to communicate orally will never be a possibility, and augmentative or alternative communication systems must be used to provide these individuals with a viable means of communication. Although much progress has been made in the application of augmentative communication, a number of critical issues remain to be addressed.

Neural prostheses implanted in various auditory centers of the central nervous system may help patients who have extensive nerve damage and are not candidates for cochlear implants. Development and assessment of cochlear and neural prostheses need to be continued. These efforts should include studies of enhanced signal processing techniques for application to neural prostheses, as well as to hearing aids that can benefit a large percentage of the hearing impaired.

Advances in prosthetic and orthotic devices have improved ambulation of children with amputation, limb deformities or muscle weakness. However, in adulthood, individuals who have used these devices are developing specific nerve and muscle disorders caused by long-term use of the devices. Research on secondary complications of using an assistive device is needed to prevent additional physical impairments and subsequent disabling conditions.

The restoration of functional capacities through pharmacological intervention may be significantly influenced by the developmental stage of the individuals in treatment. It is essential to select pharmacological interventions that are age-specific and duration-sensitive.

Effective drug dose, site of drug action, mechanism of drug action and side effects of drugs may differ among infants, children, adolescents and adults who have central nervous system disorders. Future research will focus on developing maximally effective drug therapy for different neurological impairments at different ages.



Research scientists at the United States Department of Agriculture are examining how diet and nutrition affect brain function. Vitamin B₆ status, for example, can influence the natural startle reflex, which is being tested here.

Environmental Impacts on the Human Brain

The brain regulates the function of every organ system in the body, ensuring that the internal environment which surrounds each cell in every organ is maintained at constant and optimal conditions. To effect this level of control, the brain constantly processes information necessary to make appropriate adjustments in the activity of each system. Part of that information is derived from the changes that might occur in the internal environment, and part is received from the external environment. The sensory systems gather information from the external environment, and this information is then processed at either the conscious or subconscious level. The environment can also be the source of additional inputs that may affect the internal environment. These external environmental factors can be physical (e.g., noise, light, radiation, temperature), chemical (e.g., toxins, drugs, solvents, pesticides), biological (e.g., HIV-1), or psychological (stress). These environmental factors, therefore, can alter the function and activity of different organs, including the brain.

■ Accomplishments

During the last decade significant progress has been made in understanding how environmental factors cause nervous system dysfunction. Through both animal and human studies, scientists are uncovering the basic mechanisms underlying neurotoxic events, and this new understanding has improved the ability to predict relationships between exposure and neurotoxic responses. For example, research has led to a greater understanding of the mechanisms of cognitive dysfunction produced by mercury and lead and the neurological deficits produced by organophosphate insecticides. The mechanisms involved in some chemically induced axonal neuropathies have also been elucidated. Recently, scientists discovered the mechanism of cognitive dysfunction produced by injection of domoic acid, an excitatory amino acid.

Recent studies suggest that dietary levels of mineral elements (boron, copper, zinc, iron and manganese) can influence both cognitive and psychomotor function. For example, mood states have been found to be related to dietary consumption and blood concentrations of aluminum, calcium, copper, iron, magnesium and zinc in healthy adult women. Iron deficiency exacerbates the toxic effects of lead. Nutrition studies of trace elements have revealed a relationship between trace elements and changes in sleep patterns. Relationships also have been observed between brain electrical activity (EEG) and dietary copper, serum iron and ferritin, zinc balance and thyroid func-

tion in healthy adult men and women participating in long-term studies. It appears clear that the dietary and nutritional status of the individual must be considered as well as other environmental factors that may affect brain function and the central nervous system.

An important physical factor that affects brain function is environmental lighting. Research over the last decade has convincingly shown that the seasonal alterations in mood, sleep and performance seen in individuals with seasonal affective disorder are due to the shortening of the daylight hours during the winter months. Seasonal affective disorder can be effectively treated by exposure to bright light at the appropriate time of day. Recently, investigators have shown that light is a very important environmental factor for regulation of human circadian rhythms and reproductive function. These studies have resulted in

important applications for treatment of conditions such as sleep disorders, jet lag and problems related to shift-work.

Environmental factors can directly or indirectly affect food or water intake or metabolism. Scientists have shown that the developing organism is very sensitive to malnutrition. Investigators are greatly interested in determining whether the nervous system can recover fully after a short-lived, early nutritional insult.

Research with children revealed a correlation between a long-term nutritionally deficient diet and lower IQ scores. Years after the nutritional deficiency, several residual deficits in affected children were observed.

Investigators have demonstrated that a number of chemicals, including drugs of abuse, polychlorinated biphenyls, methylmercury and lead, can adversely affect newborns. Malformations of the nervous system comprise over half of all human congenital abnormalities, necessitating investigations of their epidemiology, causes and pathogenesis. Developmental exposure to environmental factors such as lead can also produce functional deficiencies in children, including performance deficits and decreased IQ.

Scientists have recently linked environmental factors to the etiology of certain neurodegenerative diseases. For example, it has been established that ingestion of certain foods, such as the drought-resistant grain pea, can cause lathyrism, a disease affecting motor neurons. The active ingredient in the pea appears to be an indigenous excitatory amino acid. Another example is the compound MPTP, first produced during attempts to synthesize a "street drug." In younger humans and experimental animals, MPTP causes pathological changes and clinical symptoms very similar to those of Parkinson's disease.

Research has provided several developmental and adult neurotoxicity testing methods to evaluate a wide range of behavioral, neurochemical and neuroanatomical endpoints associated with environmental factors. In addition, scientists also have developed a battery of neurological



The National Institute of Environmental Health Sciences supports and conducts research to uncover how external factors such as stress and environmental toxins can disrupt nervous system function and, in turn, that of other body systems

and behavioral tests and used them to assess the potential neurotoxicity produced by a number of chemicals, including toxic air pollutants, contaminants of drinking water, pesticides, metals and solvents. In some instances, basic biomedical research has resulted in a clear understanding of the progression of disease from the molecular lesion to the clinical neurotoxic disorder.

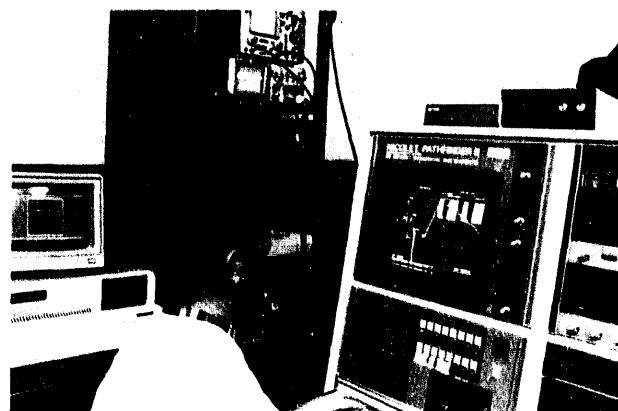
■ Future Plans and Potential Benefits

Evidence accumulated in recent years strongly suggests that an interaction between environmental factors and neural structures such as the brain may precipitate a series of events leading to the development of human neurological disorders. The use of modern molecular and cellular biological approaches will help investigators develop new methods for evaluating the actions of neurotoxic agents. These techniques may also lead to the development of new approaches to prevent, diagnose and treat the resulting neural disorders.

Future research will emphasize studies on the basic cellular and molecular mechanisms underlying neural communication, neuroendocrine regulation and signal transduction in order to provide a basis for understanding how neurotoxic agents can cause specific neurological disorders, and affect cognitive, behavioral or reproductive functions. Development of a mechanistic understanding of neurotoxicity will facilitate the discovery of biologic markers of exposure to toxicants, as well as markers of early, subclinical neurotoxic effects. Integrated information gained from these studies can provide important clues for the development of appropriate diagnostic and therapeutic strategies to prevent or treat environmentally related disorders.

In the future, scientists also will analyze *in vitro* test methods designed to identify mechanisms of action of neurotoxicants at the cellular level, and determine how effectively these systems predict chronic effects in whole animals and humans. The development of adequate *in vitro* test systems will also provide an important and valuable alternative to *in vivo* testing to evaluate neurotoxicity of compounds that may not induce changes measurable by more conventional, whole-animal techniques.

Future studies also will collect more data on the extent to which neurologic diseases and psychiatric disorders are the result of exposure to toxic environmental agents. Clinical evaluation of neurotoxic illness and epidemiologic surveillance of populations at high risk for neurotoxicity have been inadequate. Existing surveillance systems will be modified to provide better data on neurologic and psychiatric disorders likely to be of environmental origin. Physicians and other health care providers should be made more aware of the prevalence of suspected environmentally and occupationally caused neurotoxicity.



Aided by modern computer graphics, this scientist at the Environmental Protection Agency analyzes a brain wave pattern from a patient who underwent visual stimulation. By measuring specific characteristics of such brain waves, scientists can identify normal and impaired function in the brain's visual centers.

An important aspect in future research will be the identification of exposed populations and the evaluation of those bearing an unusual susceptibility to environmental factors. For instance, it is generally believed that children are more susceptible than adults to some neurotoxicants and that early exposure may accelerate the aging process. In addition, older populations are believed to be at greater risk than the young. Future research will focus on the possibility that long-term, low-level exposures to environmental factors can result in neurodegenerative disease following a long latency after the initial insult.

In the coming decade it will be important to focus on the mechanisms by which the exposure to environmental factors during pregnancy can have an adverse effect on fetal development. The advances in understanding normal neural development will provide a baseline for identifying the mechanisms by which exposure to environmental factors during pregnancy can result in disorders of the human fetus, especially those disorders occurring in the nervous system.

Studies with children have underscored the importance of trying to link early nutrition with later outcome. Because cognitive development is dependent on genetic as well as environmental factors and because the relationship of the host to the environment is an interactive one, it is difficult to draw conclusions about how a nutritional insult will affect any one individual. Comparative studies of differing populations having similar nutritional insults will give clues about how the brain reacts to such adverse conditions.

International cooperative research includes studies of humans who have been exposed to radiation. Recent findings in these studies indicate that exposure to radiation may affect the normal migration of neurons during fetal development. Future research may contribute to an understanding of the mechanisms of neural migration and the effects of environmental agents such as radiation on these mechanisms.

The expected benefits of further research with animal models, particularly non-human primates such as rhesus monkeys, derive in large part from the striking similarities in biobehavioral responses to stress between rhesus monkeys and human infants and children. Some display extreme biobehavioral responses to mild environmental stressors and appear to be at substantial risk for developing a variety of behavioral and health problems later in life. Additional insights from the use of a non-human primate model come from the opportunity to study genetic-environmental interactions directly as they shape developmental trajectories, as well as to examine possible interactions and feedback loops among a variety of behavioral and physiological systems in the same individuals throughout development.

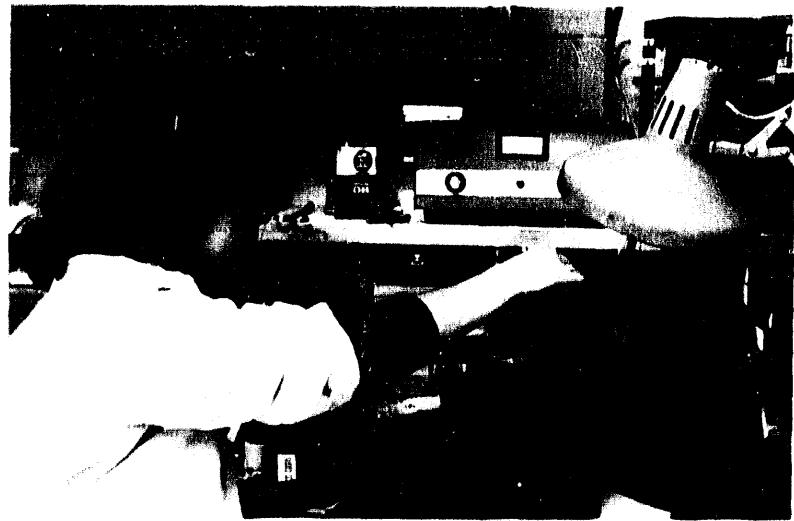
Hearing loss attributable to hazardous noise levels is on the rise in our society: more than 20 million Americans are exposed on a regular basis to industrial or recreational noise that could result in hearing loss. Hazardous noise exposure is at least partially responsible for more than 35 percent of the 28 million cases of hearing loss in this country—hearing loss which could be completely prevented. Molecular biologists have recently found evidence that heat-shock pro-

teins formed in the inner ear in response to moderate levels of sound may provide some protection against noise. Indeed, preliminary evidence suggests that the ear may be "conditioned" to withstand the effects of loud noise with little permanent effect on hearing. Thus, another factor in individual susceptibility to noise may be the ability to form and retain heat-shock proteins in the inner ear. A major goal should be to increase awareness in the public about the hazards of noise and protect people's hearing from noise-induced impairment.

Future research will emphasize the use of newly discovered technologies to study environmental influences on brain function. Using transgenic animal models, scientists have been able to obtain neuronal cell lines that maintain the characteristics of normal neurons. These cell lines will be used to evaluate how environmental toxins and other factors affect the function of key neuronal systems at the cellular and molecular level. Computer-based image analysis will be used to study the development of the structural complexity of neurons as they are affected by environmental factors, including chemicals, physical factors and biological agents such as HIV-1 and its proteins. It is anticipated that this research will provide insight into mechanisms of synaptic transmission, input effects on circuit development, and identification of those molecules that promote or retard neuronal integrity.

Recent research has suggested that some progressive neurodegenerative disorders may be related to long-term exposure to environmental factors. For example, the exposure to pesticides has been associated with Parkinson's disease, while aluminum has been implicated in the etiology of Alzheimer's disease. Although the involvement of environmental factors in these neurodegenerative disorders has not been definitely established, it is clear that exposure to some chemicals can result in a neurological syndrome similar to naturally occurring neurodegenerative disease. There is also evidence linking diet to neurodegenerative disorders. Future studies will be needed to elucidate the relationship between the chronic exposure to common environmental factors and neurological disease.

Research in the future will focus on reducing the uncertainty associated with predicting human health risk from experimental animal data. There is a need to develop and use tests based on chemical mechanisms of action and structure-activity relationships to identify and characterize potential neurotoxicants. In addition, a need exists to develop risk assessments for new environmental agents, such as those derived through biotechnology.



An investigator prepares brain tissue for sectioning and mounting on microscope slides. New staining techniques have increased our understanding of how brain tissue is damaged by toxic compounds and disease.

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Decade of the Brain Program Activities

AGENCY/PROGRAM	AID	CDC	DOD	DOE	DVA	ED
Human behavior & mental disorders	Communication research for health behavior	Health risk behaviors, HIV, dementia	Decision-making under stress	Differential diagnosis of dementia	Schizophrenia imaging, post-trauma stress	Natural history of behavioral disorders
Communication & sensory disorders	Micronutrients, blindness prevention	Surveillance systems	Computational vision, bioacoustic processing, sensory/motor control		Auditory & visual disorders	Adaptive equipment
Learning & memory		Childhood lead poisoning	Plasticity, neural & machine intelligence			Early childhood cognitive retraining
Addiction		Fetal exposure		Nuclear medicine evaluations	Addictive disorders, substance abuse	
Brain & spinal cord damage		Epidemiology, immunotoxicology, prevention, treatment, rehabilitation	Neurotoxin, chemical & biodefense cell biology	Stereotactic radiosurgery, localization of seizure foci	Regeneration, training of medical personnel, neurobiology	Trauma
Development	Prevention of childhood malnutrition	Epidemiology, occupational exposure		Genetic code/gene expression		Mental retardation
Aging	Demography & epidemiology of aging risk factors	Risk factors, morbidity, mortality		Nuclear medicine differential diagnoses	Dementia imaging, behavioral studies	Maintenance of function
Restoration of function	Prosthetics (low cost)	Neurologic & behavioral sequelae	Neural regeneration	Radiotherapy for brain tumors	Rehabilitation, robotics, artificial limbs, sensory aids	Rehabilitation
Environmental impacts		Environmental impacts of neurotoxic agents		Neurotoxic agents		

EPA	FIC	NASA	NEI	NIA	NIMAA	NICHD
Chemical-induced mental disorders	International cooperation in biomedical research	Crew behavior & performance in space	Psycho-physics	Alzheimer's assessment instruments	Alcoholic dementia	Developmental psychology
Alterations in sensory function	(")	Neurosensory response to gravity changes	Oculomotor system vision processing	Age-related changes, pre-psychosis language & age vs. pathology		Dyslexia
Chemical-induced cognitive dysfunction	(")			Cognition vs. neural mechanism	Effects of alcohol	Cognitive development, learning disabilities
	(")				Genes & environment	Fetal exposure
Chemical-induced neuropathology	(")		Neuro-ophthalmology, diabetic retinopathy	Programmed cell death		Spina bifida
Developmental neurotoxicology	(")	Effect of gravity on development	Strabismus, amblyopia, myopia		Fetal alcohol syndrome	Mental retardation, SIDS, nutrition
Accelerated aging	(")		Glaucoma, cataracts, macular degeneration	Alzheimer's	Effect of alcohol with increasing aging	
Toxicant-induced regeneration	(")	Restore vestibular & neuromotor control	Low vision rehabilitation	Strategies for the aged & prostheses, improving sleep		Mental retardation
Neurotoxic agents	(")					

NIDA	NIDCD	NIHHS	NIMH	NINDS	NSF	USDA
Comorbid- ity, drug- seeking behavior	Communication behavior & perfor- mance	Chemical- induced behavior & mental dis- orders	Schizo- phrenia, depressive disorders, behaviors, mental dis- orders	Brain func- tion & behavior	Behavioral endocrinol- ogy/develop- mental psy- chology	Nutrition, physiological function, performance
Stimulus properties of drugs	Hearing, speech, voice, lan- guage, bal- ance, chemi- cal senses	Neuro- sensory responses to environmental agents	Cognitive science	Neurobio- logy of cog- nition, funda- mental studies of sensory sys- tems	Transduc- tion infor- mation entry, com- putational linguistics	
Operant & classical con- ditioning	Language & learning dis- orders, plas- ticity	Chemical- induced learning & memory dis- orders	Cognitive science	Brain processing, storage & retrieval	Synaptic plasticity, mechanism of attention	
Brain- reward mechanisms	Prenatal & acquired toxic effects		Comorbidity (mental dis- orders & addiction)	Cellular mechanisms	Addictive behavior, social psy- chology	
Drug- induced neuro- toxicity	Aphasia, motor speech dis- orders	Chemical- induced neuro- pathology	Brain dam- age & men- tal disorders	Stroke, brain & spinal cord injury, multiple sclerosis, epilepsy	Motor behavior, physiology, anatomy	
Fetal effects	Neural substrates of senses & communica- tion	Develop- mental neu- rotoxicolo- gy, disorders of puberty	Childhood depression, autism	Genetic & developmen- tal disorders	Neuro- genetics, cell lineage develop- ment	Hormone- neurohormone interac- tions, nutrition & develop- ment
Medications develop- ment, reha- bilitation of addicts	Biochemical, physiologic, anatomical effects	Environ- mental triggers & senescence, excitotoxins & brain function	Mental & behavioral disorders in the aged	Alzheimer's, Parkinson's, Hunting- ton's	Biochemical, physiologic, anatomical effects	Nutrition & aging
	Prostheses, regrowth, augmented communica- tion	Nutritional intervention in ameliorat- ing toxicity	Drugs, implants, psychosocial rehabilita- tion	Nerve regrowth, implants, prostheses	Bioengineer- ing, prothe- ses, regenera- tion	
		Neurotoxic agents	Social/psy- chological/ environmen- tal influ- ences on brain func- tion	Neurotoxins		Environ- mental stim- ulation of neurophysi- ology

END

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