

what is neuroscience?

Neuroscience is the term applied to research on how the nervous system works and how it is affected by disease. The complexity of behavior is reflected in the complexity of the body's most sophisticated control system: the nervous system. The central nervous system (the brain and spinal cord) is composed of more than 10 billion nerve cells and 100 billion supporting cells. Nerve cells are arranged in specific circuits in precise anatomical arrangements. How nerve cells work individually to conduct electrical signals, or in con-

cert to result in behavior, thought, and consciousness, are questions addressed by research in neuroscience. Neuroscience also contributes to several medical disciplines. Diseases primarily affecting the nervous system afflict 50 million Americans; these diseases are the focus of research in neurology, psychiatry, neurosurgery, and other medical fields.

Interdisciplinary nature of neuroscience

The character of research in neuroscience has been defined by its interdisciplinary nature. The objects of study—behavior, biology, electrical phenomena, membrane biophysics, and diverse medical applications—do not fit easily into traditional academic disciplines. As a consequence, neuroscience has drawn on talent from such diverse fields as anatomy, physiology, physics, electronics, genetics, biochemistry, optics, pharmacology, ethology, psychology, neurology, psychiatry, neurosurgery, internal medicine, and information science.

Although early studies of the electrical properties of individual cells depended on advances in electronics, extensive knowledge of natural history, especially marine biology, was equally important for neuroscience research. Study of such marine organisms as squids, lobsters, and horseshoe crabs has proved invaluable in neuroscience research. This curious aspect of neuroscience is due to many “experiments of nature” in marine organisms that render them especially appropriate for the study of neural phenomena. One good example of this is the “electric eel,” *Torpedo californicum*, which uses a special organ in its body to store electrical charge for stunning enemies and prey. The electrical organ uses the same chemical for cell-to-cell communication that humans use for normal muscular contraction. This special organ has provided a plentiful, much needed source of receptor protein for studying how muscles contract and investigating the human disease myasthenia gravis. A number of important scientific and medical discoveries thus derive from the study of this bizarre creature of the hydrosphere.

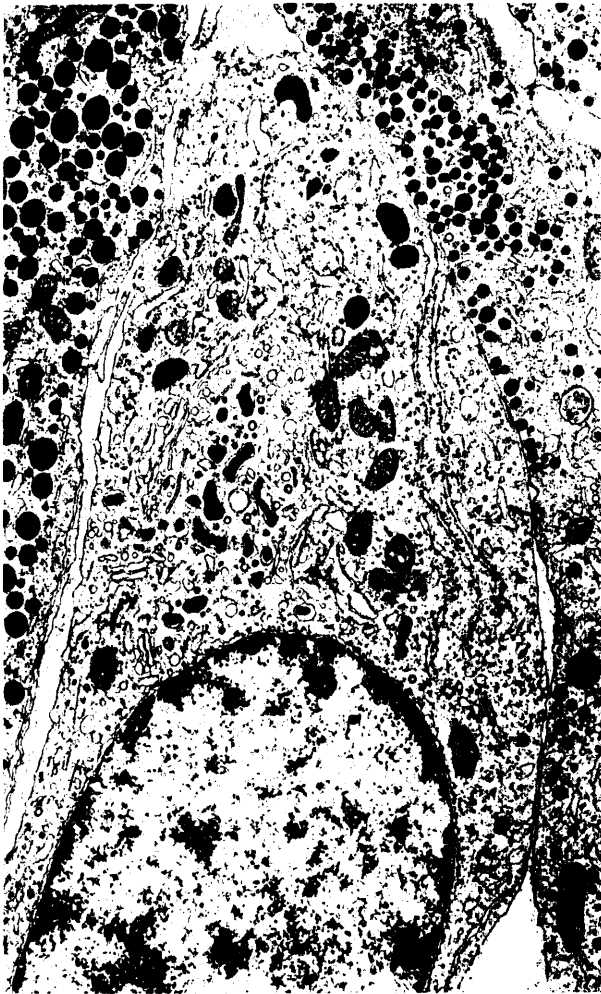


Photo credit: Dennis Landis, Department of Neurology, Massachusetts General Hospital

Photograph from an electron microscope of a cell that secretes the hormone prolactin from the pituitary gland of a rat

Neuroscience investigators have borrowed extensively from the fields of mathematics and physics to explain the interactions of molecules, cells, and networks of cells. Most recently, neuroscience has been blended with the fields of molecular biology, genetics, and biochemistry. Many of the most dramatic recent advances in neuroscience were based on fundamental new techniques developed in the fields of molecular genetics and biochemistry.

Neuroscience encompasses the study of how nerve cells are born and die in roundworms, how leech nerve cells act in concert to produce eating and reproductive behaviors, how pesticides work on the insect nervous system, and how Alzheimer disease causes dementia.

Basic concepts of neuroscience

The study of neuroscience is unified by certain basic concepts (2):

- Behavior, perception, and cognition are results of integrated actions of networks of nerve cells.
- The activities of nerve cell networks are characterized by extremely precise anatomical specificity and enormous complexity. Understanding of neural phenomena will depend

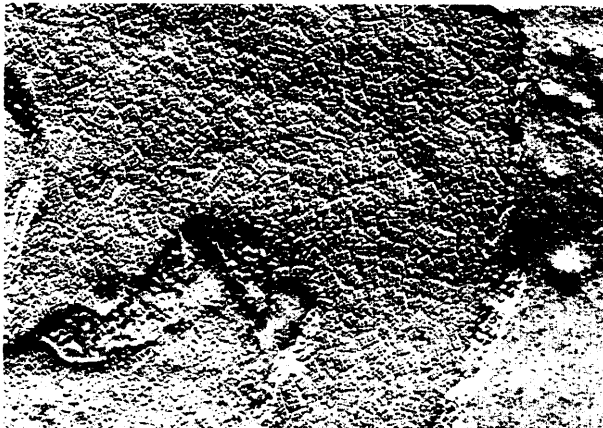


Photo credit: *Dennis Landis, Department of Neurology, Massachusetts General Hospital*

The specialized membrane of an astrocyte—a support cell of the central nervous system—in the mouse. This is taken from an area near the blood supply to the brain that prevents toxic materials from crossing into the brain from the bloodstream

on explication of how such anatomic connections are made.

- Understanding of nerve cell networks also depends on knowledge about cell-to-cell communication between individual nerve cells.
- Electrical properties of individual cells are important in the transmission of impulses and in intercellular communication.
- The electrical properties of nerve and muscle cells are controlled by molecules on the surface of the cell (ion channels and specific receptors).

Scientists believe that behavior arises from many cells working in concert. The basic precepts of neuroscience have been derived from studying the electrical properties of individual nerve cells. The classic work of scientists in the 1940's and 1950's was concerned largely with describing the way nerve and muscle cell membranes could propagate electrical impulses. Over the next two decades, scientists discovered many of the mechanisms involved in the journey of an impulse along a single nerve cell. The next major task was to describe the way nerve cells communicate. The ideas underlying neurotransmission* were established in the following decades and continue to evolve rapidly today. The list of chemicals involved in neurotransmission, once limited to a handful of simple compounds, has rapidly lengthened to include complex proteins and protein fragments, hormones, and other types of molecules.

Wide variety of technologies used in neuroscience

The advance of knowledge in neuroscience has depended, in large part, on new technologies. Scientists can now watch the functioning brain, investigate the behavior of whole organisms by studying molecular interactions, obtain electrical measurements of events in single nerve cells, and perform computer analysis of events in nerve cell

*In a process called neurotransmission, a nerve cell excites another nerve cell through precise anatomical connections called synapses. A specific chemical called a neurotransmitter is released by the sending cell into the synapse and attaches itself to receptor molecules on a receiving cell. Attachment of the neurotransmitter to the receptor causes electrical changes in the receiving cell, in a neural chain reaction.

networks. New drugs allow analysis of molecular events affecting the electrical properties of nerve cells.

New methods of visualizing the human brain without invasive procedures rely on developments in electronics, organic chemistry, numerical modeling, and computers. Investigation of nerve cells' electrical properties has required new types of electronic amplifiers and tools for manipulating fine instruments. Enlarged capacity for electronic memory has assisted greatly in the anal-

ysis of electronic data from multiple nerve cells and in reconstructing images from series of electron-microscope photographs of individual nerve cells. Recombinant DNA (rDNA) techniques have permitted the study of genes important in nerve cell function, and monoclonal antibodies (MAb) * promise to revolutionize understanding of how nerve cells work at the molecular level.

*Monoclonal antibodies are molecules produced by new laboratory techniques. They are useful for purification and identification of specific proteins and for other purposes.

Medical impacts of neuroscience

Neurological and psychiatric diseases

The study of psychiatric and neurological illness has a long and colorful history. Ancient Greek physicians knew that brain damage could lead to aberrant behavior. Precise definition of the anatomy of the nervous system and correlation of anatomy to specific neural functions were important parts of European medicine early in the 20th century. Freud presented theories about subconscious mental processes, while others were describing the first correlations between diseases and anatomic changes in the brain. These correlations led to new diagnostic categories and facilitated differentiation of groups of patients that once had been categorized together. Refined diagnosis made it possible to introduce new therapies for specific groups.

The introduction of drugs to treat neurological and psychiatric diseases began relatively recently. New drug treatments have been developed for some important disorders, although these treatments are not complete. Effective treatments for Parkinson disease, depression, manic-depressive illness, insomnia, pain, epilepsy, and acute anxiety have led to optimism that other diseases also may prove treatable and that present treatments might be improved.

The potential for improvement of current therapies is great. There is no effective treatment or means of prevention for many of the most prevalent and costly diseases; for example, there is a

great need for effective prevention or treatment of Alzheimer disease, which affects over a million older Americans and is a major source of need for long-term care. Treatments for depression, anxiety, insomnia, and other disorders also can be further improved by reducing adverse effects of present treatments, or by reaching those who do not respond to current therapies.

Advances also can be anticipated in neurosurgical techniques, rehabilitation therapies for injury to the brain and spinal cord, and replacement of limbs and sensory organs. Research in nerve regeneration, leg and arm replacement, and sophisticated hearing and seeing devices someday may lead to effective compensation for lost abilities. New technologies for visualizing the brain have led to less risky and more effective ways to detect brain tumors, areas of tissue death due to stroke, and patterns of activity associated with epilepsy and organic brain diseases. There has been a dramatic growth in knowledge about molecular and cellular aspects of pain. Some of the most important relationships between the brain and the body's other control systems (e.g., the various glands that make up the endocrine system) have been elucidated only in the last decade.

The recent history of treatment for schizophrenia illustrates the complex interactions between scientific advance, medical treatment, and public policy. Many schizophrenic patients who formerly were institutionalized can now undergo drug

treatment outside mental hospitals. New drug therapies have encouraged public policies intended to reduce the number of patients in mental hospitals. Such policies have been highly successful: there has been substantial depopulation of mental institutions (3). However, reinstitutionalization of psychiatric patients has brought with it some social costs of incomplete treatment. Current drugs tend to improve the symptoms of hallucination and delusion but do not correct other symptoms of apathy, withdrawal, and lack of motivation (4). Patients are “better but not well” (5). Many patients now released to participate in society are not capable mentally of doing so but are not offered the option of institutional care (3). Although drug treatment of schizophrenia has reduced some Federal and State health care expenditures through depopulation of mental institutions, the policy goal of deinstitutionalization has not yet led to equitable or optimal care of psychiatric patients.

The medical, social, and public policy interactions regarding schizophrenia treatment underscore the point that while neuroscience can improve the medical treatment of many diseases, medical care is only one factor in the effective management of disease. Some of the concepts regarding public policy and schizophrenia might be applied as well to other disorders that affect mental function, such as Alzheimer disease and severe depression.

Other diseases

The usefulness of neuroscience research is not restricted to neurological and psychiatric diseases. There is great potential for advances in managing fertility and infertility, cardiovascular disease, infectious and parasitic diseases, developmental disabilities, and immunologic disorders.

In the developed world, cardiovascular diseases are a major source of illness and death, especially in older individuals. The development of new drugs for cardiovascular diseases has depended, in large part, on advances in understanding the physiology and electrical properties of nerve and muscle cells. Two classes of drugs recently introduced for the treatment of hypertension and cardiovascular disease—the so called “beta blockers”

and “calcium antagonists”—were tools for the study of nerve and muscle cells for years before they were shown to have clinical applications (6).

In the developing world, parasitic diseases are serious health problems. Ancylostomiasis (hookworm infection) affects 20 to 25 percent of mankind. A group of drugs working at specific nerve receptors constitute the primary treatment of this disease. The drugs work by interfering with neurotransmission, paralyzing the worm. Because the drugs do not enter the brain or spinal cord of the host, only the worm is affected (7,8).

Schistosomiasis, a parasitic disease, affects over 200 million people, mainly in Asia, Latin America, and Africa, where it is a major cause of death and disability. Treatment involves paralyzing the parasite with drugs similar to hypnotic/sedative agents currently in use (8).

The treatment of both of these major parasitic diseases thus has depended on increased understanding of the interactions between nerve cells and their neurotransmitter chemicals. Development of these new treatments also has depended on understanding the neurobiology of invertebrate organisms, an area of research that is not as well funded as study in mammals and other higher animals. The use of chemicals to combat parasitic diseases is an important example of how neuroscience research on seemingly unimportant invertebrate organisms has led to widespread human benefits.

Fertility and infertility are concerns in both the developed and developing worlds. Advances in neuroscience, focusing on the neural mechanisms in the hypothalamus that regulate hormone release and reproductive function, promise to yield effective and safe methods of managing fertility and infertility for both men and women (9).

Behavioral medicine, the study of how behavior relates to disease, is another widely applicable field. Research on how to control smoking, alcoholism, and stress may improve prevention of cancer, liver disease, and cardiovascular illness; further study might help explain the brain's influences over the body's defense mechanisms. Addiction has a behavioral component whose study might lead to better control of drug and substance abuse. Research in behavioral medicine may allow

better control of eating disorders by controlling appetite or by identifying environmental variables that trigger inappropriate eating.

Nutritional factors affect brain development and function. Most nutritional disorders involve several different organ systems, but the nervous system often is affected first or most severely. For example, malnutrition during embryonic, fetal, and early infant development leads to permanently diminished mental capacity. Severe deficiency of most water-soluble vitamins leads to well-defined neurological syndromes manifested by behavioral, sensory, and motor disabilities. Good nutrition depends on an adequate number of meals, well-balanced meals, and economic and social mechanisms for providing food to the population. Neuroscience research can help identify some of the factors that influence eating behavior, set minimum dietary standards for nutrients, and clarify the consequences of nutritional deficiency.

Issues affecting development of drugs for the nervous system

The length of patent protection from competing manufacturers, the development of drugs for rare diseases, and the effects of international competition in the pharmaceutical industry are issues related to the development of all drugs. While these issues are important, they are not discussed here because they are not directly related to neuroscience. There are, however, several unique issues related to drugs that specifically affect the nervous system,

Central nervous system drugs constitute a large fraction of the total pharmaceutical market compared with other drug types, but development costs also are higher (10). The costs of development are believed by some to be due to the absence of adequate animal models for study of behavioral effects. The period used for U.S. Food and Drug Administration (FDA) approval for drug use is longer for drugs affecting mental function than for other classes of drugs, such as cardiovascular drugs and antibiotics (11). It is claimed that psychoactive drugs are regulated more stringently for demonstrated efficacy than other drugs because the illnesses and disorders that are

treated often are not life-threatening, and fewer undesirable side effects are permissible (12).

Indications for use of psychoactive drugs have been confused in the past because of the difficulty in establishing definitive psychiatric diagnosis. Difficulties in defining diagnoses and symptoms have complicated the testing and use of psychoactive **drugs (u)**, although recently published standards for diagnosis of mental illness may promote consistency (13).

The ethical problem of research using mentally incompetent patients is another impediment to development of psychoactive drugs. Such patients include those suffering from dementia and severe psychiatric disease—precisely those patients for whom many nervous system drugs are most needed.

Many psychoactive drugs have been introduced in the last two decades. There is promise of developing new drugs to affect “higher” functions such as memory and learning, but dramatic new developments probably are not imminent (14,15). Some drugs intended to affect mental abilities, particularly among demented patients, are being tested now in the United States and Europe. Psychoactive agents now under development do not appear much more powerful than existing drugs. Thus, fears of new social problems from recreational and occupational use may be premature (14). It is **impossible** to predict whether drugs that substantially improve mental function can be developed in the future; there is insufficient evidence now to make such a judgment (15).

There is a higher potential for abuse with psychoactive drugs than with other types of drugs. This leads to several regulatory effects that are unique to psychoactive drugs. For example, those drugs deemed prone to abuse are registered with the Drug Enforcement Administration of the U.S. Department of Justice, which may restrict dissemination and monitor use.

Support for biomedical research

The Federal Government, through Congress and numerous executive agencies, is the primary source of support for biomedical research in general and neuroscience in particular. Appro-

priations for biomedical research were over \$4 billion in fiscal year 1983 and included approximately \$500 million for neuroscience research (see app. A). The funding of biomedical research is a public investment intended to increase understanding of diseases and biological mechanisms for the future benefit of citizens. Some of the justifications for such research are the opportunities to:

- reduce future morbidity and mortality, and associated medical costs;
- increase industrial productivity by reducing loss of time from work due to illness;
- augment public health through prevention based on new knowledge; and
- improve medical treatment based on scientific advances.

In addition to these features that are shared by neuroscience and other fields of biomedical research, there are some aspects of neuroscience research that distinguish it from other areas.

The prevalence of neurological and psychiatric disease is increasing, largely due to aging of the U.S. population. Disorders such as Alzheimer disease and depression, for example, are becoming more common because they are more frequent in the expanding elderly population. The increasing prevalence of neurological and psychiatric diseases contrasts with decreasing mortality from some other types of diseases such as hypertension, atherosclerosis, and cancers other than lung cancer. This rising prevalence of brain diseases may increase future health care costs.

Neuroscience is distinctive in its rapid growth and its potential for continued growth. Technical innovations and institutional arrangements for research in neuroscience have led to acceleration of the scientific pace in the last decade. New technologies promise to enhance further the power of scientific investigation of the nervous system. Creation of new neuroscience programs and departments focuses academic attention on this young scientific field. Growth requires support from the Federal Government and private industry.

Neuroscience has reached its adolescence at a time of budget austerity, in contrast to the field of cancer research, which grew when Federal funding for science was rapidly expanding. This suggests that neuroscience now may be restrained because the resources available to support it are constrained by budgetary pressures.

Research in neuroscience is highly interdisciplinary. This makes institutional arrangements at universities and other research centers more difficult for neuroscience than for research along disciplinary lines. It is more difficult to sustain support for an activity that has no departmental or other institutional home. In recent years, the trend in funding agencies has been to focus, even more than in the past, on investigator-initiated grants rather than institutional grants for interdisciplinary research. This has made sustenance and creation of centers of excellence for neuroscience more difficult.

Training of personnel to do research in neuroscience is of particular concern. Funding for training programs has been cut more severely than for research grants. A recent study by NSF, in cooperation with the Society for Neuroscience, found that despite rapid expansion of scientific opportunities, jobs for young investigators are limited, and training programs do not appear to be growing as rapidly as in the recent past. * It is significant that only five universities had separate neuroscience departments—most degrees in neuroscience were granted by other departments in traditional disciplines.

Recent advances in technology and basic knowledge have rapidly expanded the frontiers of neuroscience. The field thus may have great scientific potential at present, so that investment now could be especially productive.

*Most research positions are at universities, and most universities are not hiring. This is a major reason for limitation of new job opportunities.

Social impacts

Neurotoxic exposure

An important topic in any discussion of Federal policy involving neuroscience is damage to the nervous system from toxic substances, or neurotoxicity. Injury to the nervous system is manifested by irritability, personality changes, fatigue, lack of control of body movement, loss of sensation, and other symptoms. Often, symptoms of neurotoxic injury are wrongly ascribed to aging of the individual or to social factors. Damage to nerves can occur from food, beverages, drugs, environmental agents, or occupational exposure to toxic agents. Many drugs have neurological side effects, particularly those intended to affect some aspect of neural or cardiovascular function (many of these drugs are prescribed deliberately to affect one part of the nervous system, but also may affect another part in an undesirable manner). Metals and chemicals in the environment can affect individuals who inhale contaminated air or ingest contaminated water and food. Occupational exposure to neurotoxic substances also is quite common.

Clinical research and toxicity testing already have established that “roughly one-fourth of the chemicals most frequently encountered in industry and of known toxicologic significance have documented neurotoxic effects [and] this represents only a small part of the total problem” (16). Discoveries of the severe effects of heavy metals, some pesticides, and many organic solvents have led to improved industrial and environmental controls and have prevented recurrence of many of the disasters of the early industrial period. Many instances of neurotoxic injury probably have not been discovered yet, hidden because of the difficulty of establishing a link between changes in cognition or behavior and the presence of an occupational or environmental toxic substance.

Neurotoxicity during brain development.—Early human development, particularly during the embryonic and fetal stages, is a period of special vulnerability to neurotoxic exposure. Such exposure can be tragic because of the limited ability of the nervous system to recover from ser-

ious insults. In general, nerve cells cannot be regenerated; remaining cells can only readjust their connections to compensate for lost cells. Such compensation is often incomplete. Therefore, damage done to embryonic, fetal, and infant brains often is associated with permanent disability. Examples of this are the lifelong mental retardation associated with maternal malnutrition during pregnancy (17), and long-lasting mental incapacity due to toxic lead exposure during infancy.

Interactions between chemicals encountered at work or in the environment and other factors also may damage the developing nervous system. Animal experiments have shown that effects due to alcohol can be exacerbated by exposure to organic solvents (18). Such interactions would be difficult to detect in normal human settings because of the large number of potentially confounding variables.

Difficulties in detecting neurotoxic damage.—one reason that the problem of neurotoxic exposure has not been identified earlier is the difficulty in detecting neural damage. The symptoms of toxic injury to the nervous system often are changes in behavior, mood, and personality that may be wrongly ascribed to factors other than chemical exposure. For example, the “fetal alcohol syndrome” was *not* discovered because of its deleterious effect on brain development that leads to permanent retardation but because of distinctive facial and skeletal abnormalities in affected infants (19). The mental effects of prenatal alcohol exposure, which cause the most serious long-term disability and lead to most of the costs of care, only later were identified. In adults, many neurotoxic symptoms are ascribed to stress, personal problems, or aging, rather than to chemical or other environmental exposures. Symptoms of irritability, forgetfulness, and hostility often *may* be due to factors other than chemical exposure, but the relative importance of the various factors cannot be ascertained because so little is known about the frequency of neurotoxic injury,

Another factor that makes detection of neurotoxic injury difficult is the long period between time of first exposure and identification of the first definite symptoms. Most industrial neurotoxic hazards have been found because of relatively quick development of symptoms associated with use of a particular chemical, or massive exposure levels. Examples of rapidly developing toxicity include episodes of chlordecone (Kepone) exposure in a Virginia plant in 1975 and methyl-N-butyl ketone (MBK) toxicity in an Ohio coated-fabrics factory in 1973 (20). Massive exposure is exemplified by the "lead palsy" identified decades ago, when lead levels were so high that workers showed overt signs of disease within months,

In the tragedy of Minamata Bay in Japan, 121 people were afflicted by a mysterious illness, and 46 died (20). Many infants were born with irreversible mental retardation, and many fishermen were affected. The pattern of exposure suggested contamination of the water or food supply. Investigative work revealed mercury compounds emanating from effluent discharged into the bay by a local factory that was using mercury compounds in chemical production. The industrial waste was entering the marine ecosystem, eventually contaminating fish and shellfish. Local residents had ingested the contaminated fish. The Minamata Bay episode was only one of several instances of mercury poisoning identified in Japan and Iran in the 1970's.

The Minamata Bay episode is a classic example of the complexity of neurotoxic exposure. Social factors, dietary habits, industrial practices, ecological processes, occupational exposures, and developmental vulnerabilities of infants and fetuses were all part of this web of interactions. Yet the Minamata Bay exposure had a better chance of detection than other types of exposure because the effects of toxic injury appeared quickly in the local population. Rapid identification was possible because the symptoms were severe and could be related easily to a change in an industrial process.

The more insidious effects of **long-term**, low-level exposure are not known for most chemicals. The syndrome of "mad hatters" who were exposed chronically to toxic levels of mercury com-

pounds in the manufacture of hats, is an example of long-term exposure leading to behavioral abnormality that has been known for almost a century. Workers in factories in the United States, however, still suffer from tremors due to mercury poisoning (21). Neurotoxic effects of other chemicals may not be identified if neural damage occurs only after long periods of exposure. Research on this aspect of neurotoxicity is still in its infancy.

One possible, but as yet unproven, hypothesis relates acid rain to nerve cell injury. Congressional hearings were held recently by the Human Services Subcommittee of the House Select Committee on Aging to look into a possible, but as yet highly speculative, association between acid rain and certain neurological illnesses. The link is postulated to be due to increased leaching of metals, such as aluminum, from soils under acidic conditions. The hearings demonstrated the need for increased research into possible links between chronic brain disease and environmental factors.

Scientific activity has led to improved methods of detecting neurotoxic injury. A recent survey of behavioral toxicology studies found more than 90 publications, almost all of which had been published since 1973 (22). New methods of detection based on changes in animal behavior have progressed, and the use of drugs to increase sensitivity of animal tests and tissue preparations also is making headway (23). Such tests, however, have not been incorporated into standard protocols analogous to those used in testing potential mutagenic and carcinogenic agents.

Progress in detecting and testing for neurotoxic injury is important because effective regulation of chemicals, drugs, and other potential toxic agents must rely on findings based on reliable scientific methods.

Federal regulation and research. * —Even if methods of detection can be found, there is concern that Federal agencies may not be capable of promulgating and enforcing regulations for neurotoxicity. The two largest Federal agencies involved in regulating toxic exposure are the

*See app. B for details on Federal agencies involved in regulation and research of neurotoxic exposure.

Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA) of the Department of Labor. Some congressional oversight has touched on issues related to neurotoxicity. For example, the Subcommittee on Department Operations, Research, and Foreign Agriculture of the House Committee on Agriculture recently heard testimony that the resources of EPA may be insufficient to review adequately the needed studies or to process the registration and testing of pesticides. Pesticides may be important sources of environmental neurotoxicity to those in the general population who eat treated food, and of occupational exposure to those engaged in pesticide production or agriculture. *

Urban dwellers are also subject to chemicals that adhere to or are incorporated into foodstuffs. Some countries allow use of agents that are banned in the United States, and importation of foods from these countries may be a source of neurotoxicity. Vegetables and other foods grown in urban gardens maybe contaminated by deliberate garden spraying or from treatment of trees, shrubs, and grasses located nearby. Spraying of trees, golf courses, and garden plants, and exposure to heavy metals from industry and automobile emissions all contribute to neurotoxic residues that might accumulate on food grown in urban environments.

Deliberate neurotoxic exposure.—There is one category of neurotoxic exposure that individuals impose upon themselves. The use of neurotoxic inhalants to alter consciousness is one example of deliberate exposure. “Glue sniffing” and inhalation of other organic solvents is common, especially among some innerwity populations. Inhalation of many organic solvents yields a temporary feeling of euphoria but may damage the nervous system and other organs (24). such substance abuse is just one form of selfdestructive behavior, analogous to other examples of drug abuse listed below.

● Pesticides are of particular concern because many act by affecting the transmission of impulses in the insect nervous system. There is concern that pesticides may not be completely specific to the pest but may also affect people and animals.

Alcohol

Alcohol is one of the most common neurotoxins in this country; it is estimated that 9 percent of adults in the United States drink heavily on a regular basis (25). Half of all automobile accidents probably involve alcohol abuse, and the annual economic cost of alcohol use in the United States may be as high as \$120 billion (25). Most of the costs are incurred as health costs for treating alcoholism or loss of productivity due to illness and alcohol-related disability.

In addition to the usual symptoms of alcohol use, there are also numerous long-term health consequences of heavy use. There are at least 15 neurological syndromes associated with alcohol, as well as numerous blood, liver, and cardiovascular disorders. Certain cancers and infectious diseases are also more common or more lethal in alcoholic patients. Adults are not alone in their exposure to damage from alcohol use: women who drink during pregnancy can cause mental and physical disability in the fetus. “Fetal alcohol syndrome” is a severe example of such toxicity (26).

Military preparedness also may be jeopardized by alcohol use. A recent Department of Defense survey concluded that 34 percent of all military personnel suffer alcohol-related productivity loss (27).

Alcohol causes economic, social, military, medical, and family problems. Many of the effects of alcohol that lead to lost productivity and increased susceptibility to accidents are due to its neurotoxicity. This is characteristic of many drugs of abuse: they are used because they affect mental function, yet may be dangerous for the same reason.

Drug abuse and addiction

Use of drugs that affect the brain, such as hallucinogens, depressants, stimulants, and tranquilizers, is common in the United States. A recent article in the New England *Journal of Medicine*—referred to the use of psychoactive drugs in America as a “modern epidemic,” noting that a

half million Americans are addicted to heroin, as many as 13 million may have used amphetamines without medical supervision, and more than 50 million have used marijuana at least once (28). The same article reported that 11 percent of high school seniors use marijuana daily, and more than 8 million Americans have used it over 100 times. Evidence suggests that use of illicit psychoactive drugs has increased about twentyfold in the last two decades (28).

Addiction to opiate drugs is an extreme example of drug abuse. Addiction appears to be due to a combination of behavioral and biological components. Behavioral medicine may lead to further understanding of addiction; basic neuroscience may contribute to understanding the biology underlying addiction. Research findings over the last half decade have led to startling insights into the molecules involved in cells affected by drugs such as morphine and heroin. Dramatic acceleration of progress has followed the discovery of natural molecules, endorphins and enkephalins, that are manufactured by the brain to affect the same receptors influenced by opiate drugs (29).

It is possible that treatment of physical dependency on drugs might improve as a result of a better understanding of addiction. Increased knowledge may permit identification of individual variations in biological susceptibility to certain agents. Neuroscience by itself cannot resolve the problem of psychoactive drug abuse, whose roots may be social as well as biological, but advances in understanding and treatment are needed to underpin social interventions and public policy.

Neuroscience may also help clarify the important distinction between drug addiction that has serious public health and social consequences (e.g., encouraging crime to support the biological need for drug use) and "recreational" use that has few deleterious effects. Drug abuse ranges from caffeine to heroin, and public policy is based, in part, on differences in biological effects of the agents. Caffeine use is not regulated, but heroin production, sale, and use are illegal. Between these two extremes, there is widespread disagreement as to what should be regulated. For example, there is wide variation among the States in enforcement of alcohol and marijuana statutes.

This diversity reflects disagreement over the seriousness assigned to use of particular drugs. Further research in neuroscience may narrow the range of disagreement by providing data on biological effects. However, physiological and medical effects are only two of many criteria used for determining "serious" drug abuse in different contexts and cultures.

Biological rhythms and work schedules

New work patterns demanded by modern manufacturing and service industries have led to rising rates of shift work. A significant fraction of the American work force, 27 percent of male workers and a slightly lower fraction of female workers, is subject to disruption of sleep, increased incidence of gastrointestinal distress, and difficulties in socializing with families and friends as a consequence of night and shift work (30). Further, it has been shown that worker errors are more common during late-night shifts and are concentrated in the early morning hours. For example, the accident in Reactor II at the Three Mile Island nuclear powerplant occurred during the 3 a.m. to 5 a.m. period, a time during which a highly disproportionate number of accidents occur, as demonstrated in numerous industrial studies (31).

Shift-and night-work schedules are of Federal concern because they involve worker health and safety, public safety, and industrial productivity. Many functions performed or supervised by the Federal Government, such as air traffic control at commercial airports, staffing of missile silos, and operation of nuclear powerplants, must be performed around the clock. Congressional interest in shift work was expressed recently in hearings before the Subcommittee on Investigations and Oversight of the House Committee on Science and Technology. Innovations in shift work were described, and several Federal agencies involved in protecting public safety testified on present shift-work practices. Evidence was presented showing that current shift-work practices often fail to take account of data regarding optimum work schedules and ignore recent neuroscience research on biological rhythms.

Experiments on natural circadian rhythms have led to discovery of at least two “biological clocks” that correlate with hormone levels, body temperature, sleep cycles, and attentiveness. Work schedules more closely in accord with natural biological rhythms have yielded improvements in productivity, decreased error rates, and increased worker satisfaction (32). Simple social and industrial interventions based on neuroscientific knowledge can ameliorate some problems—in this case, by merely altering the periods of rotation between shifts and changing the direction of rotation from shift to shift.

Industrial productivity

Neuroscience may help eliminate or alleviate some causes of lost worker productivity by reducing substance abuse and by identifying and preventing neurotoxic exposure among workers. Work schedules can be improved by use of principles derived from neuroscientific experiments. Education and retraining may be improved as more is discovered about learning, memory, and communication. The advance of neuroscience, therefore, probably will lead to changes not only in those industries directly linked to biology and drug development but in other industries as well.

Long-term effects on industry

International Competition.—Congressional concern for the international competitiveness of U.S. industry has increased in recent years. The relative position of the United States compared to other countries may prove important in those industries affected by neuroscience. It appears that the United States supports more activity in basic neuroscience research than any other country, much as it has had the largest national effort in molecular genetics and immunology. The high degree of development of basic science, the presence of mechanisms for training personnel, the flexibility of university-industry relations, and Federal support for basic science in the United States have proved important in the early phases of development of those industries related to biotechnology (33). The relatively good position of the United States also could prove important in any future “high tech” industrial applications

based on neuroscience. An industrial sector based on neuroscience could develop in pharmaceuticals, chemicals, or information technology and management, albeit with very different time scales. Contributions to the drug industry are likely to predate applications in information science and management.

The development of new psychoactive drugs is likely to be important for future growth of drug companies because psychopharmaceuticals provide a highly profitable and growing market. It is not clear, however, how American-based companies will fare in the competition for new psychopharmaceutical markets. A recent study by the National Academy of Engineering expressed concern that the pharmaceutical industry in the United States may be losing some of its competitive advantage over foreign industries (34). The amount of neuroscientific research in the United States might be construed to confer competitive advantage in the psychopharmaceutical sector to American companies. Yet, scientific excellence may not translate to more jobs or income for American workers. The American lead in science may be undercut by the extensive worldwide integration of pharmaceutical markets (leading to rapid international technology diffusion and less competitive advantage to the country of origin) and the relative stringency of the drug approval process in the United States (providing incentives for introduction of drugs abroad, rather than in the American market).

Creation of New Industrial Sectors.—Neuroscience also is expected to contribute to developments in other industries such as food production, pesticide manufacture, and information processing. Industrial applications of neuroscience may be analogous to other nascent high-technology applications, such as those deriving from biotechnology and semiconductors. Knowledge about human cognition may include how better to use tools such as electronic and mechanical equipment. This might lead to improved “human factors engineering” of such tools.

Future developments in agriculture may yield a second “green revolution” based on biotechnology and neuroscience. Neuroscience can contribute to development of new, more specific pesticides affecting insect nervous systems and

prepare the way for discovery of other ways to control pests, such as growth factors and airborne insect hormones. Such innovations will depend in part on studying pest behavior and biochemistry under controlled conditions with methods developed in neuroscience.

The development of an entirely new industry based on biological substrata, such as artificially grown nerve cell networks or "biochips" made by micro-organisms, may be possible in the future. Artificial intelligence programing of computers may contribute to understanding how complex information-processing networks work, possibly yielding fertile analogies for the study of nerve cell interactions. Understanding of brain function and cognitive processes, conversely, may further understanding in information science, leading to new applications. Although only general predictions can be made about the industrial development of neuroscience, it seems likely that neuroscience will prove more important in the future.

Crime and violence

Neuroscience may provide some insights into ways to prevent or better understand violence and suicide and may even allow treatment of some selected problems (when they are due to identifiable and correctable aberrations). For example, researchers recently have found that levels of 5-hydroxyindolacetic acid (5-HIAA), a byproduct of a specific neurotransmitter family, are elevated in the spinal fluid of those who have committed suicide by violent methods [35]. This finding strengthens the link between depression, which is also associated with elevation of 5-HIAA, and suicide. This knowledge, combined with highly effective drug treatments for several forms of depression, eventually may provide a method for prevention of some violent suicides. However, the use of 5-HIAA measurement as a means of identifying those who might commit suicide is highly unlikely because only a small fraction of those with the biochemical change are suicidal.

Researchers also have found 5-HIAA in some who have histories of multiple violent criminal offenses. The previously mentioned link of both aggression and suicide with depression is intriguing but also illustrates the problems associated with trying to use biochemical measurement as

a predictive tool for criminal enforcement: those prone to violence are probably only a small minority of those with elevated 5-HIAA levels.

Difficulty in using screening tests for criminal behavior has precedent. The use of chromosomal typing once was regarded as promising for detecting criminal predisposition, when some reports were published showing a relatively high incidence of a particular chromosomal finding (the presence of an extra "Y" chromosome) among prison inmates. Later studies led to abandonment of the test as a predictor of criminal behavior because they proved the method had little predictive value and its use led to unfounded stigmatization of those who had the chromosomal change without the purported proclivity for criminal violence [36].

It seems unlikely that science will provide a better predictor of criminal behavior than previous criminal behavior. However, neuroscience, in combination with the social sciences, may increase our understanding of some forms of violence. If mechanisms to preserve individual autonomy are provided, treatments tailored to the needs and wants of particular individuals someday may help to manage some forms of violent behavior. Such efforts, however, will be additions to, rather than replacements for, other mechanisms of dealing with crime and violence.

Sex differences

One area receiving renewed attention is the field of sex-difference research. There are demonstrable differences between men and women in their mathematical and geometric abilities [37], and in development of moral reasoning [38]. The extent to which these differences are due to socialization rather than physiology is a topic of ongoing controversy. Progress in behavioral neuroscience may help establish the factual basis for academic and political dispute, but the moral questions regarding social equality of both sexes will not be answered by scientific inquiry.

One particularly interesting topic arising from research into sex differences is premenstrual syndrome (PMS). PMS affects some women in the days preceding menstrual periods and is charac -

terized by fluid retention, depression, irritability, and moodiness. PMS varies widely in intensity and type of symptoms expressed. It was first reported more than half a century ago (39), and has received recent attention because courts in the United Kingdom and France have acknowledged PMS as a mitigating factor in violent crimes (40). American courts may follow their European counterparts. Interest in PMS may increase as more is learned about how hormones, including sex hormones, affect behavior and other brain functions. PMS presents a particularly thorny problem: how to balance the conflict between a desire to help those who suffer with PMS and concern that it may be used as an excuse to exclude women from certain occupations and endeavors.

There is danger of premature or misdirected application of new knowledge about sex differences. In studies that have identified differences between males and females, the findings apply to population differences, not individual differences. On some tests of mathematical ability, for example, girls' scores are lower on average than boys' scores. Within the group of boys or girls, however, there is a diversity of scores, and many individual girls do better than an average boy. The differences may not be gender-specific but only loosely associated with being biologically male or female. Public policy based on sex differences must take such heterogeneity into account. However, it is not clear how to do this fairly. The studies showing sex differences in mathematical ability have led to some suggestions about dealing differently with boys and girls for purposes of mathematics research (41) and training (42). Such recommendations must be scrutinized carefully so that individual choice is not jeopardized and public policy is not imbued with social prejudice.

It is also important that public policy not be erected on theories that are not widely shared. There is agreement that there are differences in mathematical ability, but there is no consensus that this is biologically determined, despite attempts to control for educational background in analyzing test scores. Thus, it might be premature to change educational institutions on other than an experimental basis because of knowledge about sex-related differences.

Education

Neuroscience may improve understanding of the causes of some forms of learning disability, such as autism or dyslexia. * Research on these disorders has refined understanding of the perceptual deficiencies involved. Psychological innovations have led to improved methods of teaching children with these learning disabilities (43). Further understanding in some instances may allow effective treatment or compensation by providing a basis for introduction of new teaching methods.

Behavioral science also can improve education by better characterizing the mechanisms of learning, memory, and perception in normal children and adults. Indeed, the most important long-term improvements in education may derive from discoveries about cognitive function and neural processing; knowing how the brain works may well lead to better methods of teaching.

Ethical and legal aspects of neuroscience

There are positive and negative aspects of advances in neuroscience. Public ambivalence is reflected in the different attitudes toward psychoactive drugs in two novels by Aldous Huxley. In *Brave New World*, the drug "soma" is used as a means of avoiding reality—as a method of mind control by the state. In *Mind*, psychoactive drugs are used to expand human experience benignly,

There are legal and ethical issues that derive from loss or change of mental function, in addition to concerns over the proper use of technologies that affect the brain. For example, it has taken several decades to attain general acceptance of the concept of brain death in medical circles. Several examples of ethical and legal issues relating to neuroscience are summarized here.

Public Concern Regarding Science.—Public concern regarding neuroscience is not unique; it is shared with many other sciences. There is,

● Autism is a disorder in which the individual appears to be separated from the external environment. Recent treatments have involved drugs and behavioral intervention. Dyslexia is a diminished ability to read. It can have many different causes, including trauma and stroke. One common form, found in children, appears to have an important genetic component.

for example, substantial public concern over the application and misapplication of biotechnology. The furor over laboratory and community safety of rDNA has been supplanted by fear of the use of “genetic engineering” in humans. Public apprehension about science and technology is often a mix of both rational concern about possible misuse and uncertainty about the science or technology itself. Uncertainty about the subject matter is associated with ambivalence regarding the extent to which decisions should be left to experts. In an open and democratic society, public perceptions often have Federal policy implications. *

When there is dispute over executive actions, the courts often must decide whether scientific evidence has been used properly (44). For example, Federal courts have been involved in controversies about environmental protection, worker safety standards, and public safeguards in the use of nuclear power. However, the courts are ill-equipped to make scientific judgments, and they are inefficient in regulating social activities. The courts are best suited to judging whether the decisionmaking *process* is fair and appropriate; court decisions are poor substitutes for coherent legislation (45).

At present, there is no permanent Federal institution for dealing with areas of science that are associated with public apprehension. Up to now, public concern over technologies has been dealt with on a case-by-case basis. One illustrative example concerns public perceptions of the dangers of rDNA research. Much of the controversy over rDNA might have been avoided had a mechanism already been in place for voicing public concerns and airing scientific evidence. The potential efficacy of such mechanisms has been demonstrated by the same controversy. Public fear seems to have decreased since the establishment of the Recombinant DNA Advisory Committee (RAC) at NIH.

Two important components in assuaging public apprehension seem to have been the inclusion of nonscientists on the RAC and the openness of the

process by which regulatory decisions were made (45).

Other controversies involving neuroscience have arisen over the experimental use of hallucinogens on unsuspecting patients by the Department of Defense and the Central Intelligence Agency, and the Soviet Government practice of committing dissidents to psychiatric institutions and forcibly treating them with psychoactive drugs. It thus seems highly probable that there will be future controversies based on public apprehension about some aspects of neuroscience.

Mental Competence and Informed Consent.— Ethical issues related to neuroscience are not restricted to public concerns; there are also many issues of individual rights. One recurring issue, as noted in the context of drug development, is the inability of psychiatrically disabled or demented patients to consent to medical treatment or experimental research. Demented patients cannot judge the adequacy of treatment or evaluate the risks of experimentation for themselves. Who should decide for such patients whether they should participate in a clinical trial of a drug for dementia, and what should be the standards for ensuring protection of their rights? This question is especially difficult when experimentation is unlikely to benefit the patient directly. * Determining who should decide is important, because new drugs for dementia cannot be developed without using appropriate patients. It may prove necessary to establish clear guidelines by legislation or executive action.

Current guidelines focus on the role of the family or courts in substituting judgment for the patient in question (46). In most cases, present policies are not controversial. However, for those patients without families and those who come from families whose best interests may not coincide with those of the patient, there are no formal mechanisms for making decisions. Many controversies have arisen from disagreement among family members, courts, hospitals, and health care pro-

*A statement relevant to this section was delivered by Senior Circuit Court Judge David L. Bazelon at the OTA workshop and is included as app. C to this background paper.

*Direct benefit may be unlikely either because a treatment has never been tried, and so there is no basis for expecting benefit, or because the research is intended to provide information that will allow future benefits but that will not affect care of the patient being studied.

professionals on a proper course of action. Dramatic examples of conflict about when to terminate life-sustaining treatment of mentally incompetent patients have received national media coverage. Such publicity highlights the inadequacy of present methods for dealing with the difficult ethical, moral, financial, legal, and social issues surrounding mentally incompetent individuals.

Several Federal bodies, including the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, have considered the difficult issues involved in research and treatment of those who are **demented** or psychiatrically disturbed (47). In 1978, recommendations based on commission activities were submitted to the Department of Health and Human Services regarding the use of psychosurgery and the care of those institutionalized as mentally infirm; no regulations have been issued yet by the Department.

Forcible administration of psychiatric drugs. -whether psychopharmaceuticals can, in some instances, be administered to psychiatric patients without their consent is under review by the courts (48). Advocates of rights for psychiatric patients object to institutional judgments about treatment that override the autonomous decision-making power of individuals, while others assert that such psychiatrically disturbed individuals are incapable of rational autonomous choice. Resolution of this problem will require substantial effort by those in bioethics and the law and may require new legislation.

Insanity defense against criminal prosecution.—The insanity defense against criminal prosecution has long been a subject of medical and legal disagreement (49). The validity of the legal concept of insanity is receiving renewed scrutiny, and the mechanism for verifying mental deviation is also being debated. Those in the psychiatric and legal professions are attempting to resolve the issue by developing guidelines for both psychiatric diagnosis and legal use of psychiatric opinion.

The power of the concept of abnormality.—Special mention should be made of the per-

vasive effects of the concepts of normal and abnormal as applied to mental, cognitive, and emotional states. The power of the label "abnormal" is substantial in public policy concerning mental retardation, psychiatric illness, and neurological handicaps. It is important to acknowledge the power of labeling patients so that adequate care is taken to ascertain both the validity of the label for a particular patient and the integrity of the label itself (50). The diagnosis of major psychiatric illness is associated with a multitude of medical, institutional, and social stigmata. Neuroscience can assure that differences between normal and abnormal have scientific merit; neuroscientist and others may ensure that knowledge is applied responsibly and equitably.

Animal welfare.—The use of animals for psychological and medical research and in testing of drugs and cosmetics is currently a focus of controversy. The neuroscience are involved because animals are used in many experiments on pain, recovery of neural function, and new surgical techniques. Many topics in neuroscience must be studied in higher animals, including primates, because of the need to extrapolate findings to the highly complex nervous system of humans. How to balance the need for medical and scientific progress against the moral imperative to avoid animal suffering is a problem subject to acrimonious public debate. Legislation on this topic already exists, and the need for additional regulation is being considered by several States and the Federal Government.

Other areas of potential moral disagreement.—Findings regarding the biochemistry of crime and violence may lead to ethical debate regarding appropriate public policy. Revelations about the genetics of mental disease may also engender moral controversy. Knowledge applicable to education, sex differences, substance abuse, nutrition programs, worker monitoring for toxic exposure or personal drug use, and many other social problems also may lead to difficult ethical and legal dilemmas.

Recent congressional initiatives have responded to the disbanding of the President's bioethics commission and to delays by executive agencies in implementing its recommendations. Congressional