Impacts of Neuroscience

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Impacts of Neuroscience

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Preface

Neuroscience is one of the fastest growing areas of scientific inquiry in biology. This background paper, prepared by OTA with significant contribution by the Congressional Research Service, surveys the scientific basis of research on the nervous system, identifies several medical applications, examines some of the social effects, and discusses some of the difficult ethical and political issues that may arise from discoveries in neuroscience.

This paper is part of an assessment of ***Technology and Aging in America*** that was requested by the Senate Special Committee on Aging, the House Select Committee on Aging, and endorsed by the House Committee on Education and Labor. The paper arose naturally from inquiry into diseases and conditions that affect the health of older Americans. Neuroscience research has led to new treatments for major causes of death in both the developed world (cardiovascular disease and stroke), and developing nations (parasitic diseases), in addition to advancing knowledge about neurological and psychiatric disorders. In the United States, the aging of the population provides one of the strongest incentives for research on the nervous system, because of the burden of illness imposed by several mental and organic brain disorders that become increasingly common with age, such as depression, insomnia, and Alzheimer disease.

Alzheimer disease alone affects more than 1 million Americans, and causes severe financial and emotional stress on each family that it affects. Alzheimer disease is one of the most significant causes of need for long-term care in the United States. One of the most important motives driving neuroscience research is the desire for solutions to the ravages of brain diseases like Alzheimer disease. * This background paper focuses on the status of basic neuroscience research, and was extended, in accordance with the OTA mandate, to investigate not only the current status and potential medical applications, but also to include broad social and ethical issues that might arise from such research.

• More detailed discussion of Alzheimer disease and related disorders will be found in the OTA assessment ***Technology and Aging in America*** **to be published subsequently.**

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“Until August 1983.
•● From Dec. 26, 1983,

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Introduction

Neuroscience is the study of the nervous system, how it affects behavior, and how it is affected by disease. The goal of neuroscience is to define and understand the continuum from molecule to cell to behavior. New tools available to scientists promise to clarify some of the mysteries of how behavior is related to molecular, cellular, and electrical events in the brain.

The 50 million Americans with disabilities caused by neurological and psychiatric diseases provide compelling justification for studying diseases that affect the nervous system. Damage to the nervous system from exposure to toxic agents, both at work and in the environment, is receiving renewed attention from policy makers as knowledge increases. Neuroscience research may contribute to the solution of some problems related to crime and substance abuse. * The health and productivity of the American work force may be altered by application of principles derived from neuroscience. The multiplicity of ways in which understanding human behavior can impact on society underscores the need to understand the concepts of neuroscience and how that science relates to public policy. How social and political institutions will face the challenges brought by new knowledge based on neuroscience cannot be predicted, but future options will be determined, in part, by actions taken now.

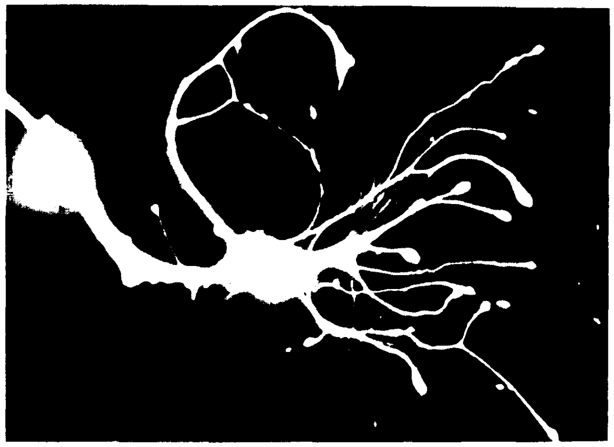

Photo credit: Stanley 8. Kater, Department of Zoology, University of Iowa

Identified neurons from *Helisoma* growing in cell culture and stained with a fluorescent antibody to reveal the presence of the transmitter serotonin

Why is neuroscience important now?

The wide diversity of applications of knowledge about behavior and other brain functions would make neuroscience interesting at any point in time. Neuroscience is especially important now because in addition to intrinsic interest in the nervous system, the field has been developing at an increasingly rapid pace. Progress over the past decade has exceeded expectations by a wide margin because of newly available scientific techniques, innovative institutional arrangements for studying the nervous system at universities, and cooperation among different scientific disciplines. Continued rapid progress is likely if present levels of support for research are maintained.

Many applications of neuroscience research may come to fruition in the next decade. Such applications may include new pharmaceutical agents, improved human factors engineering, improved pesticides, and prevention of mental disabilities due to prenatal events or toxic exposures. Improved treatment of psychiatric disorders may benefit many potential patients, Better understanding of cognitive abilities, mood, and memory may permit personal control of such functions or at least elaboration of why control is not possible.

As these applications are realized, the risks and ethical issues raised by advances in neuroscience may well become more evident and pose new questions for public policy. This background paper is an attempt to outline the scientific basis of neuroscience, to describe some of its poten-

“Substance abuse refers to deliberate use of drugs or alcohol, smoking, inhalation of solvents (“glue sniffing”), and other potentially damaging substances, tial applications, and to identify some of the ethical questions that may arise so that policymakers can better anticipate issues that may emerge.

Basis for congressional interest

Congress, and other branches of the Federal Government, are involved with neuroscience in several ways. Most funding for basic neuroscience research in the United States is channeled through agencies of the Federal Government. Payment for medical costs due to disorders affecting the brain is accomplished through the Federal agencies that manage the Medicare, Medicaid, and mental health programs. Congressional legislation has provided the backbone for regulatory actions that have reduced illness and accidents (and thus health care costs) by preventing exposure to chemicals that injure the nervous system. Congress has expressed concern for public safety in hearings on the nuclear and airline industries, citing the potential for accidents due to irregular work hours and disregard of scientific knowledge about daily biological rhythms. Use of drugs that affect mental function is a policy concern for several levels of government; regulation of drug laws, enforcement of drug abuse statutes, and payment for treatment of drug addiction are shared among Federal, State, and local governments.

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

A view of the interior and membrane of nerve cells in the cerebellum. This photograph was taken by an electron microscope of a special preparation of tissue called "freeze fracture"

The diversity of ways to apply neuroscience is reflected by the various congressional activities related to neuroscience. Over the past year, hearings on funding of neuroscience research have been held before authorizing and appropriations committees of both the U.S. House of Representatives and the U.S. Senate, Three committees have held hearings on various aspects of Alzheimer disease, Applying neuroscience research to scheduling of shift workers was the subject of one recent hearing; testimony reviewing the possible relationship between acid rain and injury to nerve cells was heard in another. Numerous hearings on environmental exposure and pesticide regulation have been convened.

The optimal mechanism for funding biomedical research has been a topic of extensive political debate. This has resulted in competing bills that mandate different levels of congressional involvement in funding decisions for the National Institutes of Health (NIH), the largest Federal agenc,y that supports biomedical research. Several different congressional bills creating a Federal agency for scientific and public discussion of topics related to biology and bioethics have been introduced.

All these congressional activities potentially affect, and are affected by, developments in neuroscience. Each of the topics summarized in this background paper is within the purview of some congressional function. One purpose of this summary is to point out the role of neuroscience research and its applications in these many congressional activities.

Several Federal agencies have identified neuroscience as an important and rapidly evolving field. In 1982, the Office of Science and Technology Policy (OSTP) selected neuroscience as one of

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

View of glial cells growing in tissue culture taken by a scanning electron microscope

seven areas for review by the National Academy of Sciences* (l). The OSTP report and others issued by branches of the Public Health Service and the National Science Foundation (NSF) document rapid advances in neuroscience research.

Relationship of this background paper to the OTA aging study

This background paper is part of an assessment of Technology and Aging in America by the Office of Technology Assessment (OTA). The prevalence of diseases affecting the brain, primarily psychiatric and neurological diseases, is projected to rise in coming decades, as the population ages, because age increases the risk of developing depression, dementia, ** and other brain disorders. Because Americans are living longer, they run greater risks of developing the diseases of old age. Greater numbers of people reaching old age and rising average longevity both contribute to the increasing prevalence of mental and neurological diseases. Developments in neuroscience therefore may affect the health and well-being of the elderly population far more than the general population. Assessment of biomedical research on neurological and psychiatric diseases is thus an integral part of understanding these future changes.

A workshop was conducted on policy implications of neuroscience research as an element of the assessment of Technology and Aging in America. Because OTA evaluates indirect, as well as direct, impacts of science and technology, participants discussed not only the medical risks and benefits of neuroscience for the elderly, but also several relevant social, medical, industrial, and public policy issues. *

Organization of this paper

Several papers on various aspects of neuroscience were written by contractors in preparation for the workshop. Some of these papers, together with chapters prepared by OTA, are printed under separate cover as ***Impacts of Neuroscience: Working Papers,*** available from the National Technical Information Service. The papers are titled:

- A Primer of Neural Function;
- Medical Impacts of Neuroscience;
- New Technologies in Neuroscience;
- Social Impacts of Neuroscience; and
- The Federal Role in Neuroscience.

This publication summarizes the above papers, gives further background on selected topics, and includes points raised in discussion at the workshop.

An introductory description of neuroscience is followed by a review of selected applications and other topics related to neuroscience, emphasizing the role of the Federal Government.

• A report was prepared by the Committee on Science, Engineering, and Public Policy (COSEPUP) of the National Academy of Sciences, highlighting some of the most promising areas of research in neuroscience. It was used to brief George Keyworth, director of OSTP, and was intended, in part, to provide guidance for the Office of Management and Budget and the White House.

•• Dementia is the diminution of higher mental functions such as memory, or the ability to calculate and think.

***Discussion of chemical and biological warfare was not included on the workshop agenda because it would be impractical for the Health and Life Sciences Division of OTA to arrange for review of classified information in an open workshop. The topic of chemical and biological warfare, while extremely important, therefore was omitted.**

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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 concert 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.

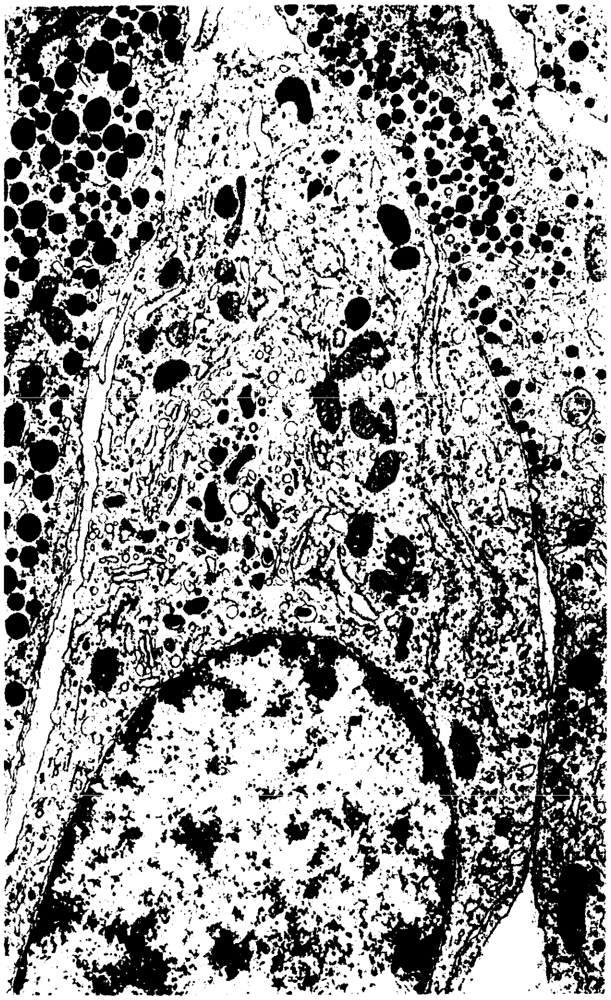


Photo credit: Dennis Landis, ***Department*** *of Neurology, Massachusetts Genera/* ***Hospital***

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

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.

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 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).

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

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 technolog es. Scientists can now watch the functioning brain, investigate the behavior of whole organisms buy 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 analysis 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 monoclinal 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. Appropriations 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 a 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 serious 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 compounds 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 caable 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 miIlion 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 encephalins, 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 persomel, 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 managment.

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.

fessionals 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 pervasive 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 activity has ranged from proposed authorization of a new commission specifically focused on human applications of molecular genetics (which might largely exclude concerns related to neuroscience) to extension of the President's commission (which disbanded in early 1983). There also has been discussion about creating a new Federal body charged with investigation of ethical concerns.

Conclusion

Progress in neuroscience research during the last few decades has led to new understanding of behavior, the functioning of the nervous system, how chemicals affect the mind, and mechanisms involved in neurological and psychiatric disorders. Many of the most important promises of neuroscience research have yet to be fulfilled; there is not yet sufficient knowledge to prevent or treat effectively many highly prevalent and disabling neurological and psychiatric diseases. Most of the risks and benefits related to social applications of neuroscience remain possibilities rather than facts. The diverse social ramifications of neuroscience applications can only be anticipated, not confidently projected. Neuroscience is an area that bears watching by scientists, health care professionals, industrialists, and policy makers. Now may be a propitious time to search for ways to translate neuroscience into application, and to anticipate the need for public discussion.

A number of neuroscience-related issues are likely to emerge. In some areas, there already appears to be sufficient scientific basis for congressional investigation. Some of these, such as the application of knowledge about biological clocks to work situations involving public safety, already have received some congressional attention. other issues, such as sex-differences research, have been identified but lack consensus regarding their importance. Still other areas of application, such as drug abuse, enhancement of productivity, development of new industries, crime prevention, and improvement of education show great promise in the long term, but the base of knowledge deriving from neuroscience research is now too scant to support Federal policy initiatives.

Some areas related to neuroscience appear to deserve congressional attention. These are characterized by their magnitude, extensive Federal involvement, and an adequate science base to support meaningful investigation. Such topics include:

- problems arising from environmental, therapeutic, and occupational exposure to neurotoxic agents, identifying numbers of people affected, scientific progress in detection, methods of prevention, and regulatory issues;
- support for basic research and personnel training in neuroscience, highlighting rapidity of progress, numbers of people who might benefit, and social and industrial applications; and
- public and governmental mechanisms for dealing with difficult ethical and legal questions related to neuroscience, including how to determine mental competence, how to make decisions for the mentally incompetent, how to control legitimate uses of drugs affecting the mind, and how to establish legal criteria for determining criminal responsibility.

Appendixes

Appendix A

Federal Support for Neuroscience Research*

Funding levels

There has been rapid growth in the field of neuroscience in the United States in the past 10 years. Membership in the Society for Neuroscience has grown from 250 members at its inception in 1971 to 8,000 in 1983.** Graduate and postgraduate programs in neuroscience have expanded by an estimated 200-300 percent during the same period (l). The most recent data suggest a leveling of the growth rate (51).

Neuroscience research is funded by a variety of executive agencies.*** In each agency, neuroscience funding priorities are related to the mission of the agency, and funds are distributed accordingly for research projects. The National Institutes of Health (NIH) receive the majority of the funds for neuroscience research. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), one of the NIH research institutes, receives over half of all Federal neuroscience research dollars. Although there are no authoritative assessments of Federal research support for neuroscience, preliminary estimates of fiscal year 1983 funding levels at each of the granting agencies, as requested from the budget office of each agency, appear in table A-1.

The fiscal year 1983 funding level for neuroscience, including behavioral research, is estimated at $503.56 million. The NINCDS appropriations history provides some indication of Federal funding trends. †

NINCDS Appropriations Levels

Fiscal year	*Actual appropriation (in millions)*
1975	$142.0
1976	144.7
1977	155,3
1978	178.4
1979	212.5
1980	242.5
1981	252.6
1982	277.7
1983	295.7

SOURCE National Institutes of Health Fiscal Year 1984 Draft Justification of Appropriation Estimates for Committee on Appropriations

Actual NINCDS appropriations increased by 108 percent between fiscal years 1975 and 1983, but this represents a real increase of only 14 percent in constant 1975 dollars (52). Further, appropriations have fallen short of earlier expectations: in 1979, when the budget needs of NINCDS were projected into the 1980's, they were targeted at $450 million in fiscal year 1983 (53), a value considerably greater than the actual appropriation of $295 million.

The Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) is the other major agency responsible for support of neuroscience. Three institutes support research and other activities related to mental health, drug abuse, and alcoholism and alcohol abuse. More than 75 percent of ADAMHA neuroscience funding is channeled through the National Institute of Mental Health (NIMH). NIMH appropriations between 1975 and 1983 increased by 64 percent overall, and funding for basic and clinical neuroscience increased by 83 percent. In constant dollars, however, there was a 7-percent decrease in overall NIMH funding. Funding for neuroscience research increased slightly, taking up an increased fraction of the total NIMH budget.

Competition for funds is keen among research scientists. In fiscal year 1982, 524 of the 1,483 approved grant applications to NINCDS were actually funded. An additional 298 grant applications were disapproved, so that 29.4 percent of all grants, or 35.3 percent of approved grants, were funded (54). Currently, the Neuroscience Program at NSF funds 20 percent of grant applications, whereas 10 years ago, 40 percent of similar applications were funded; further, the average dollar amount for grants awarded by NSF in neuroscience has dropped steadily over the past 5 years. In 1982, NIMH funded 25 percent of 1,443 total research applications in basic and clinical neuroscience. A comparable decline has been observed at most of the other NIH institutes.

Coordination

To ensure that research investigators applying for extramural funds do not receive grants from different agencies for the same research project, investigators are required to list existing and pending sources of funds on all grant applications. Computer links between NSF and NIH assure that program officers at each agency are aware of this information before

* This appendix was written primarily by Miriam Davis, Environmental Sciences Fellow at the Congressional Research Service

** The rate of growth is somewhat overestimated by these figures, because it took several years for awareness about the society to spread, and because more scientists have recently come to define their activity as neuroscience

*** See table A-1 for a list of agencies that fund neuroscience research.

† These figures differ from those in table A-1 because they include administrative costs and other costs not covered in the table.

Table A-l.—Estimated Funding Levels for Federal Neuroscience R&D Fiscal Year 1983 (miiiions of doiiars)

Agency	Extramural	Intramural	Subject areas
NIH:			
NiNCDS	$189.4	$36.3	Neuroiogicai disorders and stroke
NEI	47.2	6.1	Vision and eye disorders: basic and clinical research
NIB	10.6	2.6	Dementia and basic neuroscience
NIGHS		2.8	Basic neuroscience
NiEHS	0.3	0.78	Behavioral and neurological toxicology
Total	$247.5	$48.58	
ADAMHA:			
NIMH	$ 16.5	$22.0	Basic neuroscience
	47.6	21.4	Ciinical neuroscience
NIDA	14.0	·	Neuroscience
NIAAA	3.0	—	Biological basis of alcoholism
Total	$ 81.1	$43.4	
DOD:			
Army Medical R&D Command	$ 6.5		Chemical defense
Walter Reed Institute	—	$ 2 <	Basic neuroscience
institute of Chemical Defense	7.2	—	Chemical defense
Aviation Research Lab(Ft. Racker)	—	0.4	Vision research
AFOSR	5.7	2.5	Neurophysioiogy; vision research; chemical defense
ONR	7.4	—	Chemical defense; learning and memory; neurophysioiogy; behavior
U.S. Army Research Office	1.1	1.0	
Totai	$20.7	$ 13.1	
NSF:	21.4	—	Basic neuroscience and behavior
FDA:			
NCTR	0.06	0.71	Behavioral toxicology
CDC:			
NIOSH	0.315	0.502	Neurotoxicology
NASA:	1.0	1.0	Vestibuiar physiology
VA:	21.4	—	Aging; neurology and neurobiology;drug dependence; behavioral science; spinal cord disorders
EPA:	1.0	1.79	Neurotoxicolocw
Total	$394.48	$109.06	
		$503.56	

KEY: NIH—National institutes of Health (part of the Public Health Service of the Department of Health and Human Services)
- NINCDS—National Institute of Neurological and Communicative Disorders and Stroke
- NEI —National Eye Institute
- NIA —National institute on Aging
- NIGMS—National institute of General Medical Science
- NIEHS—National institute of Environmental Health Sciences

ADAMHA—Alcohol, Drug Abuse and Mental Health Administration
- NIMH—National institute of Mental Health
- NIDA—National Institute on Drug Abuse
- NIAAA—National Institute on Alcohol Abuse and Alcoholism

DOD—Department of Defense
- AFOSR—Air Force Office of Scientific Research
- ONR—Office of Naval Research

NSF—National Science Foundation
NASA—National Aeronautics and Space Administration
VA—Veterans Administration
EPA—Environmental Protection Agency
CDC—Centers for Disease Control
- NIOSH—National institute for Occupational Safety and Health

FDA—Food and Drug Administration
- NCTR—National Center for Toxicological Research

SOURCE: Individual agency budget offices.

grants are awarded. The Interagency Working Group in Neuroscience was formed to facilitate information exchange among extramural grantees. The working group consists of representatives from many of the granting agencies that sponsor neuroscience research. The meetings are voluntary and the group is not separately funded. Research in neurobehavioral toxicology at the National Institute of Environmental Health Sciences (! WEHS), the National Center for Tox - ecological Research (NCTR), and the National Institute for Occupational Safety and Health (NIOSH), is coordinated under the National Toxicology Program, which was created in 1978 to coordinate and provide information about potentially toxic chemicals.

Funding cycles and funding stability

Most Federal agencies supporting neuroscience research are funded by annual appropriations by Congress. Selected institutes and programs at NIH and ADAMHA are subject to periodic reauthorization as well.

In recent years, some members of Congress have expressed concern over problems with the annual funding cycle and about establishing the budget stability needed for long-term research and development (R&D). Discussions also have focused on the difficulty of assessing complex R&D programs annually. The General Accounting Office (GAO) has suggested that "instituting a multiyear R&D authorization process would be an important first step in improving R&D planning, budgeting, and oversight" (55). Others have expressed concern that a loss of oversight and accountability could result.

Policy questions regarding Federal support for neuroscience

Questions policymakers may face with respect to Federal support for neuroscience research include the following:

1. Is the level of funding adequate to support growth in the neuroscience field? Are current levels of support for research matched by support for training those to do the research?
2. What is the impact of a decrease in the percentage of grants that are funded? How many laboratories are closed due to lack of funds? What is the optimum number of neuroscience laboratories? What is the optimum approval and funding rate for research grants in neuroscience?
3. IS the degree of coordination among Federal agencies supporting neuroscience adequate to assure a productive and efficient use of funds? Are present mechanisms for coordination working? What are the advantages and disadvantages of funding through multiple Federal agencies?
4. Does the authorization/appropriation cycle for R&D funds hamper research productivity? Is it too cumbersome for Congress?
5. What is the level of support for basic neuroscience research by private industry? Is this growing or declining as a fraction of Federal support? Is private industry supporting certain sectors more than others (e.g., training programs, or research related to pharmacological applications)?

Appendix B

Federal Regulation of and Research on Neurotoxic Exposure

Legislation on toxic agents of many kinds provides the framework for Federal regulation of many industrial and environmental agents. Those activities relevant to regulation and research on substances toxic to the nervous system are reviewed in this appendix, Agents toxic to other organs and organ systems are regulated in a similar manner in many cases, but regulation of agents toxic to other organs is not summarized here.

Federal regulation of toxic substances, including neurotoxins

The Environmental Protection Agency [EPA) is responsible for enforcement of several laws that regulate toxic substances. The Toxic Substances Control Act (TSCA), the Clean Water Act, the Clean Air Act, the Resource Recovery and Conservation Act (RRCA) amendment to the Solid Waste Act, and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), with its sister legislation, the Federal Environmental Pesticide Control Act (FEPCA), all provide authority to regulate exposure to toxic substances. The Food and Drug Administration (FDA) regulates drugs, food, and cosmetics under the Food, Drug, and Cosmetic Act; and the Occupational Safety and Health Administration (OSHA) of the Department of Labor administers the Occupational Safety and Health Act. The major laws, agencies, and regulated entities are summarized in table B-1.

The FDA, OSHA, and EPA have enabling legislation to include setting standards for neurotoxicity in regulation of drugs and cosmetics, occupational exposures, and environmental exposures, respectively. Some of OSHA'S regulatory standards have been based partially on neurotoxic effects, and neurological side effects of drugs are monitored by FDA. However, none of these agencies has published standards for testing of neurotoxic effects. One reason for the absence of guidelines is the unsettled state of the science of measuring neurotoxicity. No consensus on standard methods for determining guidelines regarding neurotoxic exposure has been established, although there has been much recent progress. To explore the possibilities of standardizing neurotoxicity tests, the FDA has undertaken a long-term project that is examining batteries of neurotoxic tests with the goal of establishing a reliable, cheap, and effective means of testing for neurotoxic effects.

Pesticide regulation

One aspect of Federal involvement in regulation of neurotoxic chemicals that deserves special mention is the registration of pesticides. Pesticides are regulated by the EPA Office of Pesticide Programs. Proposed pesticides and pesticide ingredients are subject to EPA approval. Such approval requires testing for toxicity. However, approval for some uses can be obtained by application for emergency exemptions or provisions for "special local needs."

Table B-l. -Selected Federal Agencies and Laws Regulating Neurotoxic Exposure

Agency	Law	Application
Environmental Protection Agency	Toxic Substance Control Act	Chemical substances
	Federal Insecticide, Fungicide and Rodenticide Act	Pesticides and other antibiotic agents
	Solid Waste Act	Solid wastes (including ground water contamination)
	Clean Air Act	Airborne pollutants (including lead and gases)
	Clean Water Act	Water pollutants
Occupational Safety and Health Administration	Occupational Safety and Health Act	Occupational exposures
Food and Drug Administration	Food, Drug, and Cosmetics Act	Food, food additives, drugs, and cosmetics

SOURCE: Office of Technology Assessment.

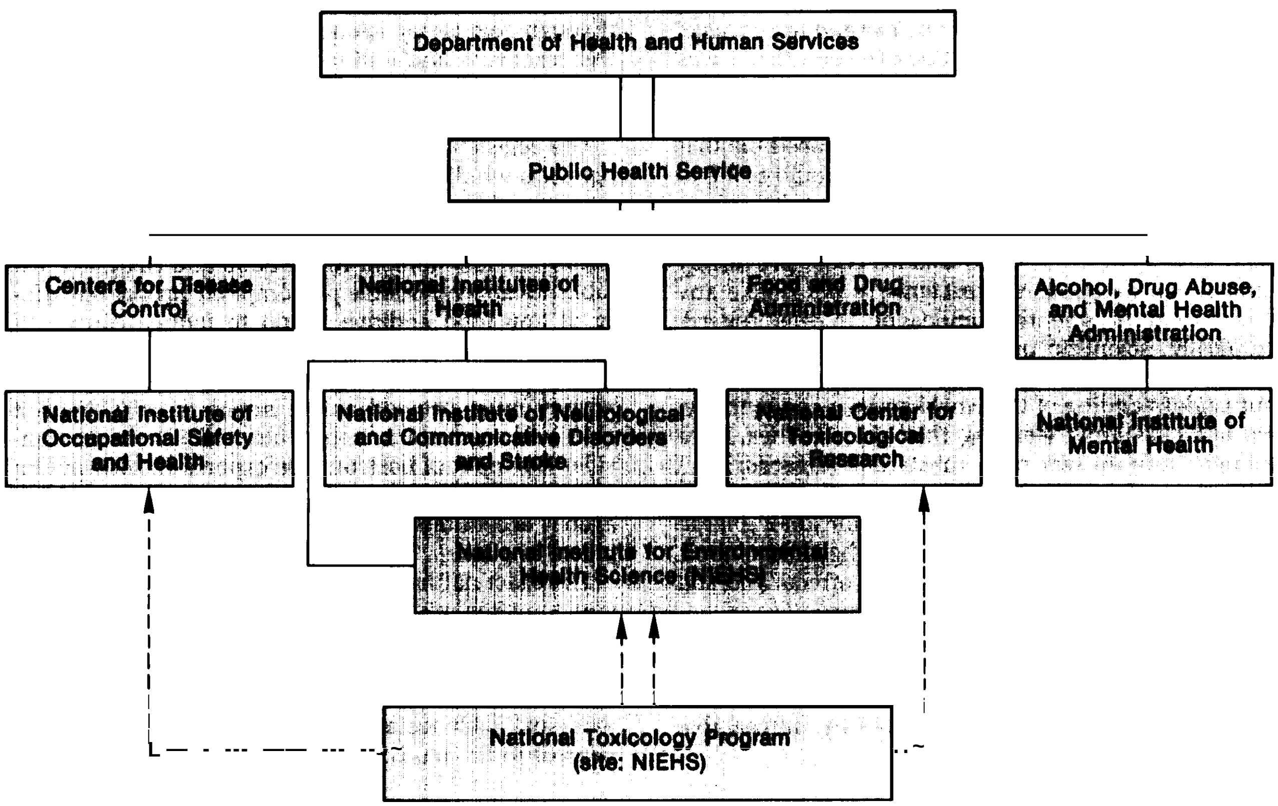
Congressional hearings on pesticide regulation and related topics were held by the Subcommittee on Department Operations Research and Foreign Agriculture of the House Committee on Agriculture on February 22-23, 1983. Documents submitted as testimony identified concerns regarding operation of the Office of Pesticide Programs at EPA. Concern was expressed about the adequacy of EPA resources to meet projected needs, methods of approval that avoid formal registration, and the scientific basis for approval of pesticides at EPA. EPA has since issued a more than 400 page set of guidelines for pesticide testing.

Federal research on toxicology, including neurotoxicology

Several Federal agencies are involved in research on neurotoxicity. All those mentioned in this paragraph and in figure B-1 are parts of the Public Health Service of the Department of Health and Human Services. The National Institute of Environmental Health Sciences (NIEHS) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), both institutes of the National Institutes of Health, conduct studies on neurotoxicity. The National Institute of Mental Health has a laboratory devoted to research on Developmental and Behavioral Neurotoxicity. The FDA has a Nationa] Center for Toxicological Research (NCTR), which is charged with developing and validating test procedures. The Centers for Disease Control include the National Institute for Occupational Safety and Health (NIOSH), which does research and provides exposure guideline recommendations to OSHA. The National Toxicology Program, headed by NIEHS, coordinates the activities of NIEHS, NCTR, and NIOSH in toxicology. The institutional arrangement of some of the major agencies doing research on neurotoxicology is shown in figure B-1.

Research on pesticides is carried out in industrial laboratories, by university scientists, and at several land-grant universities supported in part by the U.S. Department of Agriculture. Information based on research into efficacy, specificity, and health effects, including neurotoxicity, is submitted to EPA as part of the pesticide registration process.

Figure B-l.—Selected Agencies Doing Federal Research on Neurotoxicity



Appendix C

Statement by David L. Bazelon

Senior Circuit Judge
U.S. Court of Appeals for the District of Columbia Circuit
at the OTA Workshop on Impacts of Neuroscience, July 27, 1983

When I was first invited to participate on this panel, I must confess, I was bewildered. I am not a scientist, and I know virtually nothing about neuroscience. I could not begin to describe the difference between a neuron and a beta-blocker. I called Dr. Cook-Deegan, intending to decline, When he later came to my chambers, I told him that, given my lack of technical expertise, I could never presume to advise a group of distinguished physicians and scientists as to the value of a particular line of scientific research. My sole involvement with science is in my capacity as a judge. Throughout my 34-year tenure as a judge on the U.S. Court of Appeals for the District of Columbia Circuit, it has been my task to review the decisions of a great many regulatory agencies grappling with the problems posed by scientific and technological development. These decisions involve, just to name a few, the critical socioscientific issues of acid rain, cotton dust and benzene levels in the workplace, exposure to asbestos and radiation, and the disposal of nuclear and toxic waste. I tried to impress upon Dr. Cook-Deegan that I was qualified to address nothing more than the role of the courts in monitoring public policymaking in the scientific arena. Much to my surprise, he assured me that this was exactly the focus he hoped I would bring to the panel.

I hardly need to tell a group such as this that with each new advance in neuroscience come previously unforeseen dangers. Neuroscience is not unlike any other field of scientific endeavor in this regard. Ironically, scientific progress not only creates new risks but also uncovers previously unknown risks. As our understanding of the world grows exponentially, we are constantly learning that old activities, once thought safe, in fact pose substantial hazards.

For example, new psychopharmaceutical drugs, capable of controlling antisocial behavior among large numbers of psychiatric patients, have been developed. Many of the drugs have known side effects and still others may be discovered in the future.

Similarly, advances in genetics offer the hope of eliminating many genetically transmitted diseases. However, with this hope comes the threat of introducing previously unknown and presently untreatable viruses and bacteria.

Nuclear power can provide a virtually inexhaustible supply of cheap energy. It may also reduce nationwide cancer caused by burning fossil fuels. But, it *may* increase cancer risks for those living near reactors, and our inability to dispose of radioactive waste safely may place future generations in jeopardy.

The question then is not *whether we* will have risk at all, but rather how *much* risk, and *from what source.* Perhaps even more important, the question is who shall decide.

In a democracy, such choices are reserved for the public. Thus it falls to the Congress, as our representative body, to guide the direction that scientific development will take in our society. But most members of Congress are no more scientists than am I. Congress often lacks the expertise to penetrate the deep scientific mysteries at the core of important issues of public concern. Consequently, it has chosen to address the problems and opportunities of this new age through regulatory agencies. It gives those agencies the resources and authority to employ and develop expertise and to make difficult policy choices in the scientific arena.

The legislature has not, however, granted these agencies wholly unbridled discretion. First, an agency must often act within the narrow parameters of a specific statutory mandate. For example, the Delaney Clause, an amendment to the Food and Drug Act, establishes an irrebuttable presumption against the safety of any food additive found to induce cancer in animals. Second, agencies must comply with statutorily created procedural requirements. For instance, each agency must provide ample notice of all proposed rules and regulations. It must also solicit and fully consider the input of both outside experts and the public at large. Finally, Congress has attempted to ensure agency accountability by establishing a mechanism for judicial review.

The exact nature of judicial review of agency action is all too often misunderstood. This was brought home to me in a conversation with Alvin Weinberg, a pioneer of the nuclear age. "Most people," he said, "have the idea that the court weighs the arguments and the technical evidence and decides which side has come nearest to the truth. If that's not what you do, you'd better shout it from the roof tops!" So, I'm shouting it: that idea is wrong. It is wrong, first, because courts lack the technical competence to resolve scientific controversies. It is wrong, second, because courts lack the popular mandate to make the critical value choices that this kind of decisionmaking requires.

In reviewing regulatory actions, the court does not weigh again the agency's evidence and reasoning. Instead the court monitors only the process of decisionmaking, leaving factual conclusions and policy choices to the agency. The role of the judiciary is to stand outside the scientific and political debate and to ensure that all of the issues are thoroughly aired.

First, courts must ensure that an agency's interpretation and application of its statutory mandate are reasonable and that the agency is behaving in a manner that is neither arbitrary nor capricious. Second, in the realm of science, courts can insist that the data be described, hypotheses articulated, and above all, in those areas where we lack knowledge, that ignorance be confessed. In the sphere of values, courts can ask that decisionmakers explain why a particular tradeoff is acceptable. Perhaps most important, in the nether realm, at the interface of fact and value, courts can help assure that the value component of decisions is explicitly acknowledged, not hidden in quasi-scientific jargon.

I have long argued that even society's most technical decisions must be ventilated in a public forum with public input and participation. In fact, I have been pushing this theme for so long that I worry that I may be a little like my friend the amateur cellist. One evening his long-suffering wife dared ask why cellists in the orchestra "move their fingers up and down the necks of their instruments, while you always keep your fingers fixed in one place." "Ah yes," my friend replied. "I'm glad you noticed that. They are looking for the right note. I have found it!"

Full disclosure of agency decisionmaking is in everyone's best interest, including that of the decisionmakers themselves. If the decisionmaking process is open and candid, it will inspire more confidence in those who are affected, further reducing the risk that important information will be overlooked or ignored. Finally, openness will promote peer review of both factual determinations and value judgments.

Agency resistance to the requirements of full disclosure may come from either of two sources. First, in reaction to the public's often emotional response to risk, agency experts are often tempted to disguise controversial value decisions in the cloak of scientific objectivity, obscuring those decisions from political accountability. I have heard scientists held in the highest regard say that they would consider withholding information concerning risks which, in the scientist's view, are insignificant, but which might alarm the public if taken out of context. This problem is not mere speculation. I am reminded of my involvement several years ago in a hearing on the development of guidelines to regulate recombinant DNA technology in the United States. Added to the heated controversy over the substance of the guidelines themselves was an equally heated debate within the National Institutes of Health concerning the degree to which the risks and reasoning underlying the guidelines should be disclosed to the general public. Speaking to the Royal Society Conference on Recombinant DNA in England, my good friend Donald Fredrickson, the distinguished Director of the National Institutes of Health, said:

> The hearing demonstrated the difficulties of holding a town meeting on molecular biology and exposed the full range of opinions on the risks of the new technology. It was apparent that our decisions would have to run the gamut of adversarial reactions and, in the end, might well be tested in the courts. After the hearing, the voice of Judge Bazelon lingered longest in my mind: "the healthiest thing that can happen is to let it all hang out, warts and all, because if the public doesn't accept it, it just isn't worth a good damn."

It is certainly true that the public's reaction to risk is not always proportionate to the seriousness and probability of the threatened harm. Nevertheless, experts must resist the temptation to belittle these concerns, however irrational they may seem. Regulatory agencies must not turn their backs on the political process to which we commit societal decisions. Scientists, like all citizens, must play an active role in the discussion of competing values. Their special expertise will inevitably and rightly give them a persuasive voice when issues are discussed in our assemblies and on our streets, But ultimately the choices must be made in a politically responsible fashion. To those who feel the public is incapable of comprehending the issues and, so, unable to make informed value choices, I respond with the words of Thomas Jefferson:

> I know no safe depository of the ultimate powers of the society but the people themselves; and if we think them not enlightened enough to exercise their control with a wholesome discretion, the remedy is not to take it from them, but to inform their discretion.

At times, however, agency resistance to public disclosure may derive not so much from a desire to keep the public "in the dark" as from the uncertainty that characterizes much of the process of risk assessment itself. To say the least, science is often incapable of stating risks with certainty. For some activities, the magnitude of potential harm and the probability of its occurrence may be essentially unknown. For example, another of my good friends, Dr. Theodore

Puck, a noted medical researcher, tells me that toxicologists have no way of establishing with certainty the permissible, as opposed to the lethal dose of a new drug. Engineering predictions may rest on untestable assumptions, such as the behavior of materials after thousands of years. Risk estimates may depend on future contingencies of human behavior or other highly complex and unpredictable variables. Historical experience may even be totally lacking, as when the National Aeronautics and Space Administration had to fix a quarantine period for returning lunar explorers. The best risk estimates are subject to an unknown degree of residual uncertainty and may thus overstate or understate the dangers involved. Indeed, many times an agency must act in circumstances that make a crap game look as certain as death and taxes.

Those who must make practical decisions may be tempted to disregard or even suppress any lack of confidence they may have. Ignorance is messy in decisionmaking. It cannot always be stated as an objective quantity or factored into a decision as if it were a risk of known probability. Decisionmakers must assimilate data from many disciplines, And yet uncertainty detracts from simplicity of presentation, ease of understanding, and uniformity of application. To focus on uncertainties is to invite paralysis; to disclose them is to risk public misunderstanding, loss of confidence, and opposition. Even though some uncertainty is inevitable, pointing it out will always create pressures for "just one more study." But the decisionmaker knows too well that delay is also a choice, with risks of its own.

Combined with the uncertainty inherent in scientific risk assessment itself is the lack of specific guidance provided to administrative decsisionmakers. Often Congress, faced with its own inability to foresee the course that technological research and development may take, is forced to speak in broad generalities when providing statutory direction to regulatory decisionmakers. At times, legislators embroiled in conflicts of political ideology may intentionally employ vague and ambiguous language so that each faction may claim its own "victory. " I point, for example, to the "cost-benefit" analysis required of agencies by numerous statutory schemes. Such analysis often calls for controversial quantitative valuations of human life and health. It frequently presumes to compare incomparable) such as the harm of radiation exposure versus the benefits of nuclear power. And, perhaps most troubling of all, cost-benefit analysis breaks down completely at one of the most crucial points in the decisionmaking process: How can one quantify the impact of utterly unknown risks?

This quandary was vividly illustrated in the recent *Vermont Yankee* cases. Confronted with the unenviable task of quantifying the hazards posed by the construction and operation of a nuclear reactor, the agency assigned a value of zero to the risk of exposure to radioactive waste products. Apparently, this assessment was based on the assumption that some safe method of permanent waste disposal, not presently available, would be developed at some time in the future. This supposition may well prove to be correct. However, all efforts to date to develop such technology have failed miserably, and if the hypothesis that future efforts will succeed proves false, the damage could be inestimable. Yet nowhere in the agency's environmental impact statement was this assumption, or the foundations upon which it was based, explicitly revealed.

If courts reject this sort of administrative sleight-of-hand, they are not attempting to obstruct the path of scientific progress. Rather, they are merely attempting to carry out Congress's mandate that decisionmaking be honest, open, thorough, rational, and fair. As we confront the perils and promises of this scientific age, both democracy and human dignity demand that we be told of the risks, uncertainties, and value choices that are made in our names.

In primitive societies, when the need to choose between cherished but conflicting values threatened to disrupt the community, the simplest path was decision by a shaman or wizard, who claimed miraculous insight. In our time, some would invoke the special wizardry of those who wear a scientist's lab coat, a judge's black robes, or a risk assessor's business suit rather than religious garb. But the genius of our system is its checks on centers of accumulated power. Whatever its price, nothing but full disclosure can guarantee that the regulators or the new guild of risk assessors will not become the new elite.

If the Supreme Court's most recent opinion in the *Vermont Yankee* case portends a new trend of judicial indulgence toward agency nondisclosure, Congress may need to reaffirm its intention that the administrative decisionmaking process be subject to a searching and meaningful judicial review. In any event, when undertaking an assessment of technological development in neuroscience-or in any other area of scientific endeavor—the Office of Technology Assessment must take care to see that the risks are treated openly and evenhandedly, In this regard, I might note that, in the draft document we are considering today, * con-

* The draft document referred to was reviewed at the OTA workshop. Some parts of the draft are reprinted in the working papers for Impacts of Neuroscience.

siderable attention has been devoted to the benefits promised by neuroscientific advances, while treatment of the attendant risks has been confined primarily to a scant five pages in the introduction and scattered references elsewhere in the manuscript. Finally, I would like to add my own endorsement to the proposal that OTA undertake an independent assessment of the adequacy and openness of decisionmaking processes in the scientific arena.

Some may argue that society might balk if it knew just how blindly we march into the future—and at what cost. But false reassurances, unjustified confidence, and hidden agendas will only create cynicism and destroy credibility. Our people have always been prepared to accept risks and to pursue the larger good of society. Progress can hardly be achieved in any other way. Choices will be made despite uncertainty and despite the social disruptions and dislocations. To choose rationally, however, society must be informed about what is known, what is feared, what is hoped, and what is yet to be learned.

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Appendix E
References

1. Committee on Science, Engineering, and Public Policy, "Report of the Research Briefing Panel on Neuroscience" (Washington, D.C.: National Academy Press, 1983).
2. This section was prepared by OTA based on material obtained in large part through the summer course in Neurobiology of the Marine Biology Laboratory at Woods Hole, Mass. The course was sponsored by the National Institutes of Health and the Grass Foundation. Other sources include course notes prepared for Harvard Medical School by David D. Potter and Edwin J. Furshpan, and several textbooks. The books used most extensively were: E. R. Kandel and J. H. Schwartz, *Principles of Neural Science (New* York: Elsevier, 1981); and S, W. Kuffler and J. G. Nicholls, *From Neuron to Brain: A Cellular Approach to the Function of the Nervous* System (Sunderland, Mass.: Sinauer Associates, 1976).
3, Braun, P., et al., "Overview: Deinstitutionalization of Psychiatric Patients, a Critical Review of Outcome Studies," *American Journal of Psychiatry 138:736-749, 1981;* Feldman, S., "Out of the Hospital, Onto the Streets: The Overselling of Benevolence)" *The Hastings Center Report,* June 1983, pp. 5-7.
4, Sharfstein, S. S., Deputy Medical Director, American Psychiatric Association, personal communication, September 1983.
5. The phrase is taken from Dr. Gerald Klerman, cited in reference 4.
6. Fleckenstein, A., "Specific Pharmacology of Calcium in Myocardium, Cardiac Pacemakers, and Vascular Smooth Muscle," *Annual Review Pharmacology and Toxicolo# 17:149-166, 1977;* Reuter, H., "Calcium Channel Modulation by Neurotransmitters, Enzymes, and Drugs," *Nature 301:569-574, 1983.*
7. Campbell, W. C., et al., "Ivermectin: A Potent New Antiparasitic Agent," *Science 221:823-828, 1983.*
8. Wang, C. C., "Current Problems in Antiparasite Chemotherapy," *Trends in Biochemical Sciences 7:354-356,* October 1982.
9. de Kretser, D. M., "Agents for Male Fertility Control, " *Trends in Pharmacological Sciences 4:221-223,* May *1983;* Harper, M. J. K., "Prospects for New or Improved Birth Control Technologies by the Year 2000 A. D.," working paper, vol. II, pt. A, for *World Population and Fertility Planning Technologies, the Next 20 Years* (Washington, D.C.: U.S. Congress, Office of Technology Assessment, OTA-HR-157, February 1982).
10. Grabowski, H. G., and Vernon, J. M., "The Pharmaceutical Industry, " *Government and Technical Progress, a Cross-Industry Analysis,* R. R. Nelson (cd.) (New York: Pergamon Press, 1982), pp. 283-360.
11. Idanphan-Heikkila, J., "New Drug Permits," National Center for Drugs and Biological, Food and Drug Administration, Department of Health and Human Services, June 1983.
12, Molner, S., contract on drug development prepared for OTA, May 1983.
13, American Psychiatric Association, *Diagnostic and Statistical Manual, 3d* ed. (Washington, D.C.: American Psychiatric Association, 1980).
14. Bartus, R., "Workshop on Impacts of Neuroscience)" Office of Technology Assessment, July 27, 1983.
15. Personal communication from officials at the National Institute of Mental Health and National Institute on Neurological and Communicative Disorders and Stroke, August 1983.
16. Anger, W. K., "Neurobehavioral Testing of Chemicais: Impact on Recommended S~andards," *Neurobehavioral Toxicology and Teratology,* in press, 1983.
17. Cravioto, J., "Nutrition, Stimulation, Mental Development and Learning," *Nutrition Today,* September/October 1981, pp. 4-15; Correa, H., *Population, Health, Nutrition, and Development,* D. C. Heath & *Co.,1975, Pp. 15-16.*
18. Nelson, B, K., Brightwell, W. S., Setzer, J. V., and O'Donohue, T. L., "Prenatal Interactions Between Ethanol and the Industrial Solvent 2+thoxyethanol in Rats: Neurochemical Effects in Their Offspring, " *Neurobehaw"oral Toxicology and Teratology 4:395-401, 1982.*
19. Voorhees, C. V., "Environmental Assaults on the Nervous System and Human Behavior: A New Health Challenge," symposium at the Annual Meeting of the American Association for the Advancement of Science, Jan. 8, 1982; citing Smith, D. W., "The Fetal Alcohol Syndrome," *Hospital Practice,* October 1979, pp. 121-128.
20. Schaumburg, H. H., and Spencer, P. S., "Selected Outbreaks of Neurotoxic Disease," *Experimental and Clinical Neurotoxicologv,* P. S. Spencer and H. H. Schaumburg (eds.), 1980, pp. 883-889.
21. Wood, R. W., Weiss, A. B., and Weiss, B., "Hand

Tremor Induced by Exposure to Inorganic Mercury," *Archives of Environmental Health 27:249-252, 1973.*

22 Johnson, B. L., and Anger, W. K., "Behavioral Toxicology," *Environmental and Occupational Medicine,* W. N. Rom (cd.), 1983, pp. 329-350.

23 Silbergeld, E. K., "Experimental and Environmental Neurotoxins: Correlation of Behavioral and Biochemical Effects," *Behavioral Models and the Analysis of Drug Action,* M. Y. Spiegelstein and A. Levy (eds.), 1982, pp. 297-315; Silbergeld, E. K., "Current Status of Neurotoxicology, Basic and Applied)" *Trends in Neuroscience* 5:291-294, *1982.*

24. Santos, Y., personal communication from the House Select Committee on Aging. Ms. Santos cited: National Institute on Drug Abuse, Series 30, #2: *Inhalants,* National Institute on Drug Abuse Clearinghouse, Washington, D. C., July 1978; Sharp, C. W., and Brehm, M. L. (eds.), *Review of Inhalants: Euphoria to Dysfunction,* Department of Health, Education, and Welfare, Publication No. 80-553, Washington, D.C., 1977; Wyse, D. G., "Deliberate Inhalation of Hydrocarbons—A Review," *Canadian Medical Association Journal* 108:71-74, *1973;* another relevant reference is: Commission of Inquiry into the Non-Medical Use of Drugs, *Final Report,* Ottawa: Information Canada, 1973, see especially app. A-9: "Volatile Substances: Solvents and Gases. "

25. *The Effectiveness and Costs of Alcoholism Treatment,* Health Technology Case Study 22, part of the OTA Assessment of Medical Technology and Costs of the Medicare Program (Washington, D.C.: U.S. Congress, Office of Technology Assessment, OTA-HCS-22, March 1983).

26. Enloe, C. F., "Thalidomide II," *Nutrition Today,* January/February 1982, pp. 16-17.

27. Hiatt, F., "One-third in Military Affected by Alcohol," *Washington Post,* Aug. 26, 1983, p. A13.

28. Nicholi, A. M., '(The Nontherapeutic Use of Psychoactive Drugs, A Modern Epidemic)" New *England Journal of Medicine* 308:925-933, *1983.*

29. Terenius, L., "Characteristics of the Receptor for Narcotic Analgesics in Synaptic Plasma Membrane Fraction From the Rat Brain)" *Acta Pharmacologia Toxicologic* 33:377-384, *1973;* DeWied, D., and Jones, J., "Neuropeptides Derived From Pro-opiocortin, Behavioral, Physiological and Neurochemical Effects," *Physiological Review* 62:976-1059, *1982;* Marx, J. L., "Synthesizing the Opioid Peptides, " *Science* 220:395-397, 1983; Rossier, J., and Chapouthier, G., "Brain Opiates," *Endeavor, New Series* 6:168-176, *1982.*

30. Taste, D. L., et al., "Stanford Research Institute: Shift Work Practices in the United States," Department of Health, Education, and Welfare Document No. 77/148 available through the National Technical Information Service as PB-274-707, March 1977; Moore-Ede, M. C., Czeisler, C. A., and Richardson, G. S., "Circadian Timekeeping in Health and Disease: Part 2, Clinical Implications of Circadian Rhythmicity, " New *England Journal of Medicine* 309:530-536, *1983.*

31 Hearings before the Subcommittee on Oversight and Investigations, House Committee on Science and Technology, Mar. 23, 1983; Hamburg, D. A., et al., Institute of Medicine: *Health and Behavior (Washington,* D.C.: National Academy Press, 1982).

32. Czeisler, C. A., Moore-Ede, M. C., and Coleman R. M., "Rotating Shift Work Schedules That Disrupt Sleep Are Improved by Applying Circadian Principles, " *Science* 217:460-463, 1982.

33. *Commercial Biotechnology: An International Analysis* (Washington, D. C.: U.S. Congress, Office of Technology Assessment, OTA-BA-218, January 1984).

34. Pharmaceutical Panel, Committee on Technology and International Economic and Trade Issues, Office of the Foreign Secretary, National Academy of Engineering, and Commission on Engineering and Technical Systems, National Research Council, *The Competitive Status of the U.S. Pharmaceutical Industry* (Washington, D .C.: National Academy Press, 1983).

35. Brown, G. L., et al., "Aggression, Suicide, and Serotonin: Relationships to Cerebrospinal Fluid Amine Metabolizes, " *American Journal of Psychiatry* 139:741-746, *1982.*

36. Bird, S., "Social Impacts of Neuroscience, " see accompanying working papers for this report.

37. Benbow, C. P., and Stanley, J. D., "Sex Differences in Mathematical Ability: Fact or Artifact?" *Science* 210:1262-1264, 1980.

38. Gilligan, C., *In a Different Voice: Psychological Theory and Women's Development* (Cambridge, Mass.: Harvard University Press, 1982).

39. Frank, R. T., "The Hormonal Causes of Premenstrual Tension, " *Archives Neurology and Psychiatry* 26:1053-1057, *1931.*

40. Gonzalez, E. R., "Premenstrual Syndrome: An Ancient Woe Deserving of Modern Scrutiny, " *Journal of the American Medical Association 245: 1393-1396, 1981.*

41. Schafer, A. T., and Gray, M. W., "Sex and Mathematics, " *Science* 211:31, 1981.

42. "Mathematical Ability: Is Sex A Factor?" letters to *Science* 212:114-121, 1981.

43. Ross, A. O., "Behavioral Therapy With Children,"

Handbook of Psychotherapy and Behavioral Change: An Empirical Analysis (2d cd.), S.L. Garfield and A. E. Bergin (eds.) (New York: Wiley, 1978), pp. 599-602.

44. Bazelon, D. L., "Statement Delivered at Workshop on Impacts of Neuroscience," Office of Technology Assessment, July 27, 1983.
45. Bazelon, D. L., "Governing Technology: Values, Choices, and Scientific Progress, " *Technology in Society* 5:15-25, *1983.*
46. Gutheil, T. G., and Appelbaum, P. S., "Substituted Judgment: Best Interests in Disguise," *The Hastings Center Report,* June 1983, pp. 8-11.
47. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research has issued several reports related to topics influenced by neuroscience. These are listed, and are available through the Government Printing Office: *Summing Up, Defining Death, Making Health Care Decisions* (covering informed consent), *Screening and Counseling for Genetic Conditions, Implementing Human Research Regulations,* and *Protecting Human Subjects.*
48. Arkin, H. R., "Forcible Administration of Antipsychotic Medication, " *Journal of the American Medical Association* 249:2784-2785, *1983.*
49. American Psychiatric Association, statement on the insanity defense, December 1982.
50. Mercer, J. R., *Labeling the Mentally Retarded* (Berkeley, Calif.: University of California Press, 1973).
51. Gomberg, I. L., and Atelsek, F. J., *Neuroscience Personnel and Training* (Washington, D. C.: American Council on Education, 1983).
52. Matthews, W., Director, Budget Office of the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, personal communication, June 1983.
53. *National Research Strategy for Neurological and Communicative Disorders,* National Institutes of Health publication No. 79-1910, June 1979.
54. Matthews, W., Director, Budget of the National Institute on Neurological and Communicative Disorders and Stroke, National Institutes of Health, personal communication, September 1983.
55. General Accounting Office, U.S. Congress, *Multiyear Authorizations for Research and Development,* Publication No. PAD-81-61, 1981.