Chapter 4

Research and Education Programs

"There is increasing concern that basic research directed towards predicting, detecting, and understanding neurotoxicity is being neglected by government, industry, and academic researchers.

Committee on Science and Technology
U.S. House of Representatives
September 16, 1986

"I would say that the methyl n-butyl ketone outbreak was the key episode in bringing attention to the field of behavioral toxicology. That signaled a shift in thinking about behavioral problems. Before Columbus, many of us thought, 'Well, people who work with some chemicals might have trouble concentrating, or maybe even some temporary or unimportant changes. After Columbus, we could see that even relatively safe chemicals, in concentrations that pose no danger to other systems of the body, can bring serious and sometimes irreversible damage to the nervous system.

W. Kent Anger, Ph.D.
Psychology Today
July 1982

"Much more work on mechanisms of chemical neurotoxicity will be required before structure-toxicology considerations prove generally useful as a screen for neurotoxicity.

Peter Spencer, Ph.D.
"Testimony before the House Committee on Science and Technology
October 8.1985

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Increasing public concern about the effects of toxic substances on the nervous system has led to some expansion of research programs in government, academia, and industry in recent years. Even so, the research programs are relatively small, and questions are frequently raised as to whether they are capable of addressing the threat that neurotoxic substances pose to public health. The style and purpose of research differs in each of these settings, yet each makes important contributions. An optimal national research program requires effective cooperation among researchers in all sectors and an appropriate balance of effort.

This chapter describes current programs in the United States and future needs for research into the causes, extent, and consequences of exposure to neurotoxic substances. The first half of the chapter describes Federal research programs; the second half addresses research efforts under way in academia and industry. State research programs are not described in this report.

FEDERAL RESEARCH ACTIVITIES

Federal research related to neurotoxic substances is conducted primarily at the National Institutes of Health (NIH), the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), and EPA. Limited research programs are under way at the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), the Department of Energy, the Department of Agriculture, and other agencies. As indicated in table 4-1, total Federal funding for neurotoxicology -related research (excluding research related to nicotine and smoking, alcohol and alcoholism, and radiation) is $67 million. The bulk of this funding (89 percent) is through ADAMHA and NIH and tends to focus on the toxicity of drugs and the biochemical mechanisms underlying neurological and psychiatric disorders. A number of other Federal agencies and organizations provide limited funding for research related to neurotoxicity as well. Given the threat that neurotoxic substances pose to public health and the lack of knowledge of the mechanisms by which these substances exert adverse effects, OTA found that, in general, Federal research programs are not adequately addressing neurotoxicity concerns.

Environmental Protection Agency

The principal research component of EPA is the neurotoxicology Division (NTD) within the Health Effects Research Laboratory at Research Triangle Park, North Carolina. This division was organized in 1978 and has gradually grown into an effective interdisciplinary research program. A committee of EPA's Science Advisory Board recently reviewed NTD's program and described it as "the leading Federal neurotoxicology research organization" (30). NTD research programs range from development of methods to evaluate the neurotoxicity of chemicals to testing of specific substances and determining the mechanisms by which toxic substances adversely affect nervous system structure and function.

The NTD is divided into three branches: the Neurophysiology and Neuropathology Branch, the Behavior and Neurochemistry Branch, and the Systems Development Branch, which provides engineering and technical support services to the first two. Recently, the Science Advisory Board review committee recommended that consideration be given to developing a branch to focus on cellular and molecular toxicology (30)$_0$

EPA has developed a multidisciplinary program to examine how toxic substances adversely affect the nervous system. The overall program strategy stresses the development of test methods and approaches for identifying and characterizing neurotoxicity and for predicting risk to humans. Studies conducted to evaluate the cellular and molecular

Table 4-l-Federal Funding for Civilian neurotoxicity-Reiated Research

Agency	Research[a] ($ millions)
National Institutes of Health[b]	32.6
Alcohol, Drug Abuse, and Mental Health Administration[c]	26.6
Environmental Protection Agency	3.9
National Institute for Occupational Safety and Health	0.7
Food and Drug Administration	1.8
Department of Energy[d]	0.5
Department of Agriculture	0.4
Total	66.5

[a]Totals are based primarily on fiscal year 1988 data.
[b]Excludes research related to nicotine and smoking.
[c]Excludes research related to alcohol and alcoholism.
[d]Excludes research related to radiation.

SOURCE: Office of Technology Assessment, 1990.

basis for chemically induced functional changes in the central and peripheral nervous systems are designed so that effects on laboratory animals can be extrapolated to humans.

Behavioral research is aimed at evaluating autonomic, sensory, motor, and cognitive functions; developing measures to screen chemicals for neurotoxic potential; and evaluating specific behavioral processes that are disrupted by exposure to toxic substances (12). Research to determine the utility of short-term behavioral tests for measuring neurotoxic effects helps EPA regulatory program offices in the development of test guidelines. Long-term research goals include the development of animal models that can be used to predict behavioral toxicity in humans.

Cellular and molecular research focuses on locating biochemical and anatomical sites of toxicant-induced changes in the nervous system. This includes developing biochemical markers to identify the targets of toxic substances within the nervous system and performing morphological studies to determine the structural consequences of exposure to neurotoxic substances. NTD's long-term goals are to develop cellular and molecular approaches that improve neurotoxicity testing and provide a better understanding of the neurobiological basis for risk assessment.

The neurophysiology component of the research program is aimed at attaining a better understanding of how physiological processes are disrupted by neurotoxic chemicals. A primary focus is the electrophy biological evaluation of sensory systems, which allows for direct measurement of nervous system activity. Where possible, the program uses methods that have direct counterparts in human research, in order to make extrapolation easier (9).

EPA regulatory program offices need more methods of evaluating neurotoxicity, largely because of the general requirements of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA) (see ch. 7). When EPA requires industry to conduct neurotoxicity testing under TSCA, it must specify the types of tests required and the data it expects from them. At times, industry may request permission to deviate from EPA guidelines (e.g., in the case of test rule development under TSCA), but these alternative test methods must be evaluated by the Agency. NTD provides much of the technical expertise necessary to support EPA program offices in this regard.

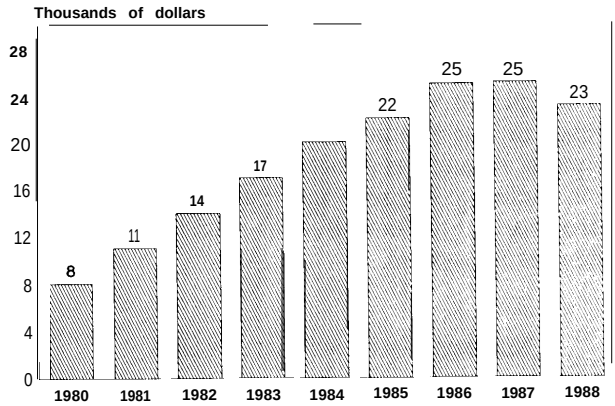
NTD is actively developing and validating two major neurotoxicity screening tests: the functional observational battery and automated testing of motor activity (see ch. 5). These tests are validated by evaluating how well they confirm the neurotoxicity of known, representative toxic substances. In this way, profiles can be developed for classes of neurotoxic chemicals.

Other approaches to neurotoxicity testing are also being developed. Electrophysiological approaches are being refined to enable investigators to monitor the excitability of individual nerve cells or groups of nerve cells or regions of the brain. Behavioral tests are being developed to assess the effects of toxic substances on memory, learning, and muscular coordination. In addition, methods are being devised to evaluate the effects of toxic substances on the developing nervous system. A variety of molecular and cellular approaches are being developed to determine the effects of toxic substances on various proteins in nerve cells (including enzymes) and on several biochemical processes, including the transport of substances along the axons of nerves. Tests designed to evaluate exposures at toxic waste sites and at chemical spills are also being developed and refined:

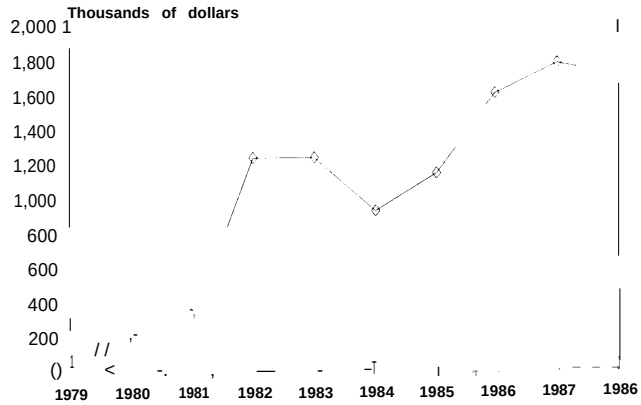
Because EPA's neurotoxicology Division is the principal Federal intramural research organization in the environmental neurotoxicology field, and because resource information on the program has been available since its inception, OTA analyzed the funding of this program in some detail. The total number of principal investigators (including some postdoctoral fellows and on-site contractors) fell to *23* in fiscal year 1988, down from 25 in fiscal years 1986 and 1987 (figure 4-1A). Funds for on-site contract support remained constant over these years at $1.7 million, up from $0.9 million in 1984 (figure 4-l B). Funds for outside contracts and cooperative agreements have fluctuated considerably (figure 4-lC). Budget stability has been a continuing administrative problem. According to the EPA Science Advisory Board committee's analysis, funds for NTD are frequently cut with little prior notice, impeding in particular the development of long-range plans. As indicated in figure 4-lD, NTD's supplies and equipment budget has dropped precipitously in recent years. In 1985, NTD allocated $23,500 in supplies and equipment to each principal investigator. In 1988, only $8,100 could be allocated (figure 4-lE). In its recent review, the Science

Figure 4-l-Resources for EPA's neurotoxicoiogy Division

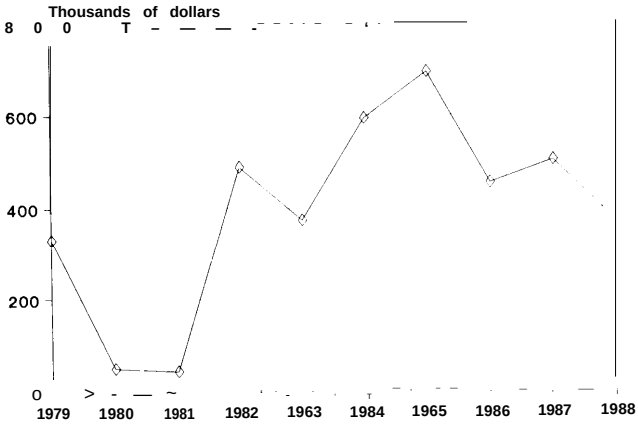
A. Total Principal Investigators



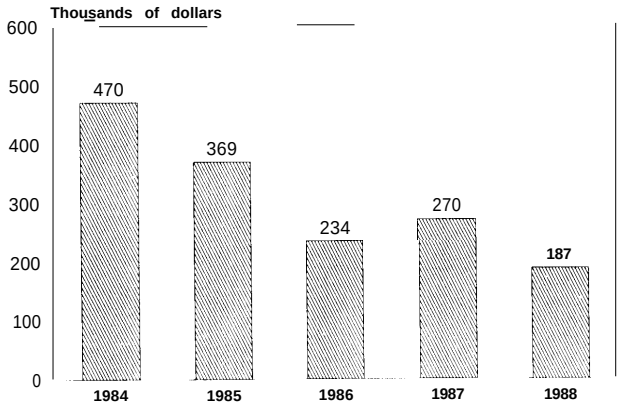
B. R&D Funds: On-site Support Contracts



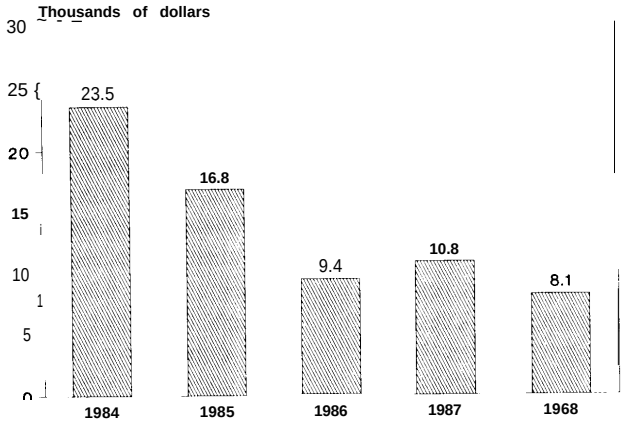
C. R&D Funds: Outside Contracts and Cooperative Agreements



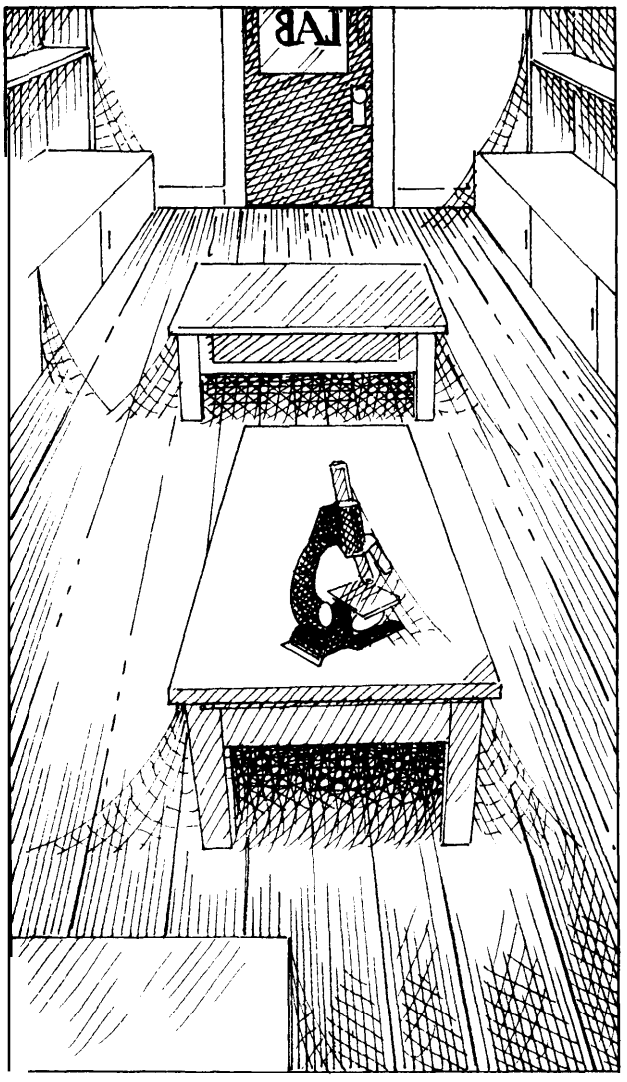
D. Funds: Supplies and Equipment



E. Supplies and Equipment per Principal Investigator



SOURCE: Based on R. Dyer, U.S. Environmental Protection Agency, personal communication, 19aa



Illustrated by: Ray Driver

Advisory Board committee described NTD's supply budget as "totally inadequate" and concluded that "important research is not carried out" because of budgetary restrictions (30).

EPA has rarely funded extramural grants in the neurotoxicology field. A substantial grants program in this area would be a valuable adjunct to its intramural program.

In recognition of the need to expand its research programs in the neurotoxicology area, EPA recently submitted to the Office of Management and Budget (OMB) a request to expand its research budget by $1.5 million. Approximately $1.0 million was requested for the development of in vitro neurotoxicology tests; another $0.5 million was requested to examine adverse effects associated with cholinesterase inhibition and the utility of cholinesterase inhibition as a biomarker for exposure. However OMB allowed no funding for either research effort. In vitro test development is often cited as a high-priority research need because of the requirement to rapidly screen toxic chemicals and to try to minimize the use of animals in research. A technical EPA panel recently recommended that the agency initiate studies to examine the relationship between cholinesterase inhibition and other adverse effects on the nervous system.

National Institutes of Health

Approximately 250 neurotoxicology -related research projects were funded by NIH in fiscal year 1988 (29). Most were funded through competitive grants to investigators in public and private institutions; the rest were conducted at NIH itself. About 80 percent of the neurotoxicology -related research (based on fiscal year 1988 expenditures) is funded through or conducted at the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina. (NIEHS is the only NH-I institute not located in Bethesda, MD.) Individual research projects averaged about $120,000. NIH expenditures on neurotoxicology -related research (excluding projects at the National Cancer Institute related to nicotine and cigarette smoking) totaled approximately $33 million. This is 0.5 percent of the total $6.5 billion ND-I research budget (44). In comparison, NIH spends approximately $1.5 billion on cancer research (44), which accounts for about 23 percent of the total research budget.

OTA found that NIH supports few programs in the field of neuroepidemiology. NIH supports a relatively large number of research projects designed to elucidate how toxic substances influence the nervous system but devotes few resources to projects examining the extent to which these substances contribute to human neurological disorders. Although the latter studies are often expensive and time-consuming, they are critical to understanding the extent to which toxic substances adversely affect public health and in determining the direction and scope of regulatory programs.

National Institute of Neurological and Communicative Disorders and Stroke[1]

In fiscal year 1988, NINCDS funded 71 research projects related to neurotoxicity. All but three of these were extramural grants to investigators at public and private institutions. Research sponsored by NINCDS covers abroad range of problems, from the level of the gene, to the cell, to the whole organism. Much of the work focuses on the mechanisms by which toxic substances adversely affect the nervous system: for example, how the flow of ions through membrane channels is altered by toxic substances, how these substances cause degeneration of nerves, how they alter other biochemical components of the nerve cell, and how toxic substances cause or contribute to neurological disorders. Several projects focused on how the chemical MPTP affects the nervous system and how it induces symptoms of Parkinson's disease. Other projects examined how therapeutic drugs influence the structure and function of the nervous system. For example, drugs used in cancer chemotherapy may adversely affect the nervous system. It is important to understand how and when this occurs in order to help maximize effects on cancerous cells and minimize damage to healthy cells.

Three intramural projects are under way at NINCDS laboratories. The largest was funded at more than $400,000 and is examining how cells derived from the brain of mammals perceive and respond to signals in their environment. A second project is examining the neurological and behavioral effects of MPTP on the monkey, and the third is devoted to the mechanism by which nerves lose their myelin sheaths.

National Institute of Environmental Health Sciences

NIEHS conducts and supports research related to the effects on human health of chemical, physical, and biological agents in the environment. NIEHS has an extensive extramural program, and it sponsored more than 80 grants related to the neurotoxicity of environmental contaminants and other substances in fiscal year 1988. The NIEHS extramural grants program is the largest source of Federal funds for research grants in the environmental neurotoxicology field. Funding for these projects amounted to nearly $12 million. NIEHS also received nearly $900,000 from EPA's Superfund program (through an interagency agreement) to support four extramural projects. In addition, NIEHS funded three neurotoxicology-related contracts totaling $755,000. The extramural projects focused on a broad range of neurotoxic substances, including metals, pesticides, solvents, natural toxins, PCBs, and other industrial chemicals. NIEHS also funded grants to several academic institutions.

Until 1987, an intramural Laboratory of Behavioral and Neurological Toxicology existed within NIEHS. Following a management change, the laboratory's emphasis shifted to basic neuroscience research (specifically, molecular and cellular neurobiology) and its name was changed to the Laboratory of Molecular and Integrative Neuroscience (LMIN). This laboratory comprises three sections and several smaller working groups, only one of which, the Neurobehavioral Section, focuses primarily on environmental neurotoxicology problems. (The neurotoxicologist who headed that section left the Institute in 1989.) An OTA analysis of fiscal year 1988 research projects found that many LMIN research projects in the neuroscience were only generally related to toxicology. Of the $3 million expended on intramural research in the neuroscience, OTA found that only about one-fourth was devoted to studies in which neurotoxicology was the primary focus. Hence, OTA found that, with the exception of the Neurobehavioral Section of LMIN, there is little distinction between intramural basic neuroscience research programs at NIEHS and those at other NIH and ADAMHA institutes. This has lead to a prominent intramural research gap at NIH in the environmental neurotoxicology field.

National Toxicology Program

The National Toxicology Program (NTP) was established in 1978 by the Secretary of the Department of Health and Human Services (DHHS) to coordinate DHHS activities related to the testing of toxic chemicals. The program was initiated to develop information about the toxicity of selected chemicals, to test selected chemicals for toxicity, to develop and validate tests and protocols, and to set priorities for testing needs and communicate results

[1]In late 1988, the National Institute of Neurological and Communicative Disorders and Stroke became the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute on Deafness and Other Communication Disorders (NIDCD) was formed. Since OTA's analysis was based on fiscal year 1988 programs, this discussion will refer to NINCDS programs.

to government agencies, the scientific community, and the public. NTP coordinates toxicology-related programs within the NIEHS, the National Institute for Occupational Safety and Health (NIOSH), and the U.S. Food and Drug Administration's (FDA) National Center for Toxicological Research (NCTR). NTP is administered by the Director of NIEHS. Program activities are overseen by an executive committee made up of the senior administrators of Federal health research and regulatory agencies. The quality of technical research programs is ensured by an independent Board of Scientific Counselors. After receiving nominations from participating Federal agencies and other public and private organizations, NTP selects chemicals to be tested. Testing is then performed by outside organizations through contract arrangements. Federal regulatory agencies have rarely requested neurotoxicity studies by NTP. From 1982 to 1988, only one substance had been nominated for neurotoxicity by the multiagency nominating committee (16). Consequently, NTP has sponsored little extramural neurotoxicology research as of fiscal year 1988. One of the few projects funded by NTP resulted in development of an automated assessment of behavior in the home cage (13,14). Intramurally, NTP has developed a neurobehavioral test battery to be used as part of its analysis of target organ toxicity. This battery will be used in a tiered testing approach to determine whether more specialized testing is necessary (43).

Within NIEHS, NTP is located under the Division of Toxicology Research and Testing. The division is composed of four branches: Carcinogenesis and Toxicologic Evaluation, Cellular and Genetic Toxicology, Chemical Pathology, and Systemic Toxicology. Toxicological concerns focus on carcinogens and mutagens (and to a limited degree on teratogens). NTP also evaluates the toxic effects of environmental agents on organ systems, including the nervous system. When health hazards are identified by NTP, additional studies characterizing the hazard are often undertaken by researchers in other government agencies, industry, and academia (16). Although the Division of Toxicology Research and Testing at NIEHS is the primary toxicological testing organization within the Federal Government, in 1988 it employed no neurotoxicologists. As of 1989, expert in-house scientific advice was provided through periodic consultation with the chief of the Neurobehavioral Section of LMIN. NTP is presently restructuring its program to address neurotoxicological concerns more effectively. Representatives of the NTP agencies participating in research efforts are preparing cooperative program plans to address neurotoxicologica.1 concerns specifically (16).

National Cancer Institute

The National Cancer Institute sponsored eight neurotoxicity-related projects in fiscal year 1988. Half of them focused on the adverse effects of cancer chemotherapy agents on the nervous system. The other four examined such problems as the induction of brain tumors by neurotoxic agents and the treatment of pain caused by cancer. Although smoking and nicotine are not included in this report, it should be noted that the Institute sponsored 64 projects related to smoking and nicotine addiction. Total funding for these 64 projects was in excess of $26 million in fiscal year 1988.

National Institute on Aging

The National Institute on Aging (NIA) sponsored 10 neurotoxicology -related research grants in fiscal year 1988. Several of these projects examine the possible role of metals in causing Alzheimer's disease; recent work has suggested that aluminum may contribute to the development of the structural changes in the brain that are characteristic of this disease. Other projects analyze age-related changes in the concentrations of excitatory amino acids (aspartate and glutamate) and the reduction in brain glutamate receptors seen in individuals with Alzheimer's disease, Two projects focus on MPTP, the aging process, and induction of Parkinson's disease-like symptoms. NIA is particularly interested in the question of why certain populations of nerve cells are particularly vulnerable to neurodegenerative diseases. Because the mechanism of cell death may be similar in different diseases, NIA is encouraging research into the molecular events underlying cell death (28). A 1988 workshop, sponsored by NIA, examined issues related to the susceptibility of the aging nervous system to infections and toxic substances.

The NIA has two intramural projects underway to examine the influence of toxic metals on aging processes and their possible role in the onset of dementia. The distribution of metals in the brain is being examined, as are the factors controlling the transport of metals across the blood-brain barrier.

In 1988, NIA sponsored a small workshop on the epidemiology of pesticide exposure and cognitive disorders in aging migrant and seasonal farmworkers. The effects on the human nervous system of long-term, low-level exposure to neurotoxic agricultural pesticides and herbicides are not known. The workship assessed the feasibility of using seasonal and migrant farmworkers, resident farmers, and others as research subjects in epidemiological studies.

National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development sponsored 11 research projects related to neurotoxicity in children in fiscal year 1988, with funding totaling approximately $1.2 million. Six of these projects focus on lead, which adversely affects the developing nervous system (see ch. 10). Two of the projects analyzed the effects of drugs used to treat epilepsy on the fetuses of mothers who must take these drugs. There is evidence that valproic acid, a drug widely used to treat epilepsy, adversely affects the nervous system of the developing fetus. The effects of valproic acid and phenytoin (another antiseizure drug) on the development of the nervous system of rhesus monkeys are being examined.

Another project is evaluating the effects of diets high in sugar or the artificial sweetener aspartame, or both, on the behavior and mental development of children. Other projects are examining mechanisms by which acrylamide, alcohol, and other substances affect the developing brain.

Division of Research Resources

The Division of Research Resources funded a total of 47 neurotoxicity-related research projects at various private and public research institutions. Projects focused on a broad range of toxic substances, including lead, pesticides, chemotherapy agents, ethanol, mercury, MPTP, and natural venoms and toxins. Total funding for these projects in fiscal year 1988 was $788,000.

Other NIH Institutes and Organizations

The National Institute of Allergy and Infectious Diseases (NIAID), National Institute of General Medical Sciences (NIGMS), National Heart, Lung, and Blood Institute (NHLBI), National Center for Nursing Research, Fogerty International Center (FIC), and National Institute of Dental Research sponsored several projects concerned with neurotoxicity. These include projects investigating the actions of a paralytic toxin from a snail (NIGMS), the adverse effects of an antibiotic on hearing (NIGMS), how bacteria degrade and avoid the effects of organophosphates (NIGMS), the possible neurotoxic effects of drugs used to treat Herpes virus infections (NIAID), the side-effects of drugs used to treat high blood pressure (NHLBI), and the effects of antipsychotic drugs on brain dopamine receptors (FIC).

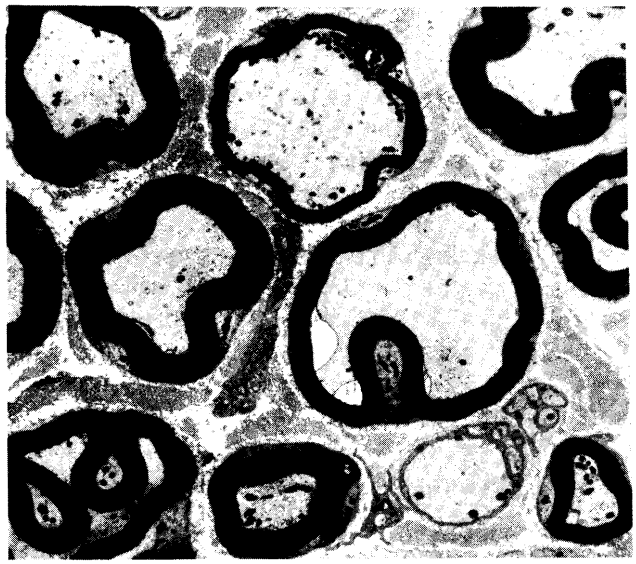


Photo credit: John O'Donoghue

This photograph illustrates the swelling of axons (dark areas) that can occur following exposure to a neurotoxic substance, in this case, 2,5-hexanedione.

National Library of Medicine

The National Library of Medicine (NLM) supports toxicological research by maintaining automated toxicology databanks and providing information services. The Toxicology Information Program was established in 1967 in response to a recommendation made by the President's Science Advisory Committee that efforts to handle toxicological information be enhanced. The NLM maintains several computerized, interactive retrieval services, including Toxline, Toxnet, and Chemline. Toxline provides information on the toxicological effects of drugs and chemicals. Toxnet contains information on potentially toxic or hazardous substances. Chemline is a chemical dictionary providing chemical names, synonyms, registry numbers, molecular formulas, and related information.

Alcohol, Drug Abuse, and Mental Health Administration

ADAMHA is composed of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). As indicated in chapter 2, OTA is excluding research on alcohol and alcoholism from this assessment; consequently, research programs at NIAAA will not be described. Both NIDA and NIMH have extensive research programs to examine the neurotoxic effects of drugs (NIDA) and the influence of neurotoxic substances on mental health (NIMH).

National Institute on Drug Abuse

NIDA sponsors a large research program related to the neurotoxicity of abused drugs. In fiscal year 1988, it funded 110 neurotoxicity-related grants. Total extramural funding was $15.5 million, or approximately $140,000 per grant. The extramural program addresses a broad range of issues from a variety of perspectives, including biochemical, pharmacological, pathological, and behavioral studies (14) and supports studies on all abused drugs. In 1988, it spent $1.5 million on in vitro studies of the neuropathological effects of drugs and on the neurotoxicity of designer drugs, cocaine, and inhaled solvents. An interagency agreement with NCTR supported studies of marijuana neurotoxicity (11).

Intramural research at NIDA is conducted at the Addiction Research Center in Baltimore, Maryland. Scientists at the center are examining the adverse effects of drugs such as MDMA (' 'ecstasy' and the related drug fenfluramine, cocaine, and THC, the active component of marijuana. The center's neurotoxicology-related research is conducted primarily in its neurobiology laboratory, but projects are also being carried out in its molecular pharmacology, preclinical pharmacology, neuropharmacology, neuroendocrinology, immunology, and cognitive sciences laboratories. Through an interagency agreement, FDA has provided the Addiction Research Center with funding to develop and validate methodologies for assessing the neurotoxicity of various drugs currently prescribed or under consideration for treatment of neuropsychiatric disorders. The center has been asked by the Drug Enforcement Administration to assess the neurotoxicity of some substances that are currently under consideration for regulatory scheduling (8). Funding for intramural neurotoxicity-related research in fiscal year 1989 was approximately $256,000 (8).

National Institute of Mental Health

A sizable portion of NIMH's research effort is devoted to neurotoxicity-related concerns. In fiscal year 1988, it funded 65 extramural grants totaling $8.6 million (excluding alcohol-related research), an average of some $132,000 per grant. These grants supported research into such issues as the mechanisms by which psychoactive drugs influence nervous system function, ways of minimizing the adverse effects of psychoactive drugs, and the contribution of toxic substances to neuropsychiatric disorders (14).

NIMH spent $2.2 million on eight major intramural research programs related to neurotoxicity. These programs are examining how toxic substances influence behavior and memory, how toxic substances may contribute to such diseases as Parkinson's disease and dementia, the mechanisms by which toxic substances disrupt biochemical processes within nerve cells, and methods of detecting toxic substances in the brain (14).

Food and Drug Administration

FDA's primary responsibility is to protect "the health of the Nation against impure and unsafe foods, drugs and cosmetics, and other potential hazards" (27). neurotoxicity research at FDA is limited in size and scope. A small research program (within one laboratory) exists in the Center for Food Safety and Applied Nutrition (CFSAN), but there is no significant research program in the Center for Drug Evaluation and Research. Several intramural research projects related to developmental neurotoxicology and one extramural project are underway at the National Center for Toxicological Research.

Center for Food Safety and Applied Nutrition

The General and Molecular Toxicology Branch of CFSAN conducts toxicological research related to food and nutrition and examines approaches to assessing health risks posed by food additives. The Neurobehavioral Toxicology Team (NBT), one of five teams within this branch, conducts neurotoxicological studies in this area. With the recent departure of a principal investigator, NBT currently consists of only the team leader, one laboratory biologist, and several laboratory assistants.

In recent years, FDA has interacted closely with EPA's Health Effects Research Laboratory, and for some time FDA has transferred funds to EPA as part of an interagency agreement (37,38). NBT is currently examining how altered ratios of carbohydrates to proteins affect brain function and how toxic chemicals are distributed in the brain. The team is also developing dog and miniature swine model systems that may eventually prove useful in predicting the effects of toxic substances on the human nervous system. Efforts are being made to assess the reliability and sensitivity of the model through a collaborative effort with investigators at NIMH.

The FDA is sponsoring three extramural projects related to aspartame and the influence of dietary amino acids on brain function (see app. A). One contractor is examining how changes in the relative concentrations of dietary amino acids affect the function of transmitters and receptors at neuronal synapses. Under an interagency agreement with FDA, NIEHS is determining whether an altered amino acid balance affects neuronal excitability or induces behavioral changes, or both, in adult and developing animals. FDA also has an interagency agreement with the Federal Aviation Administration to conduct clinical studies of the effects of aspartame on cognitive functions (39).

National Center for Toxicological Research

Located in Jefferson, Arkansas, NCTR conducts toxicology research programs that:

> . . . study the biological effects of potentially toxic chemical substances found in the" environment, emphasizing the determination of the health effects resulting from the long-term, low-level exposure to toxicants and the basic biological processes for chemical toxicants in animal organisms; develops improved methodologies and test protocols for evaluating the safety of chemical toxicants and the data that will facilitate the extrapolation of toxicological data from laboratory animals to man; and develops Center programs under the National Toxicology Program (27).

neurotoxicity-related research at NCTR currently focuses on developmental issues. NCTR is well qualified to carry out investigations of toxicological problems. Expertise is available in the areas of neurochemistry, neuropathology, neuropharmacology, behavioral pharmacology, primatology, developmental neurotoxicology, and nutritional influence on neurotoxicity.

Approximately one-third of the intramural research conducted within NCTR's Division of Reproductive and Developmental Toxicology is devoted to developmental neurotoxicology and related issues. The approximately $1.3 million intramural neurotoxicology effort includes seven to eight full-time scientists, seven to eight laboratory technicians, and two to three graduate students (32).

From fiscal year 1983 to 1988 NCTR conducted a study of the effects on primates of chronic exposure to marijuana. This project was not funded by FDA, but through an interagency agreement with NIDA. Cumulative fiscal year 1983 to 1987 funding was $1.8 million. The project was then extended for 1 year (through fiscal year 1988) at $748,000.

NCTR has the facilities, equipment, and personnel to expand interdisciplinary research in neurotoxicity and to conduct research related to therapeutic drugs and food additives, but it is currently constrained by lack of funds. NCTR recently decided to consider establishing a formal neurotoxicology unit.

Agency for Toxic Substances and Disease Registry

The Agency for Toxic Substances and Disease Registry (ATSDR) is responsible under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA, or Superfund) and the Superfund Amendments and Reauthorization Act of 1986 to carry out applied research on health effects of exposure to hazardous substances.

Hazardous waste sites contain solvents, pesticides, and metals, all of which are known to be neurotoxic. These chemicals have been released from waste sites into the air, soil, and water however, it is not known what neurotoxic effects, if any, will be caused by long-term exposure to these chemicals in the environment. The neurotoxic effects on sensitive and vulnerable populations, for example, pregnant women, young children, and the elderly, are also not understood.

ATSDR is required by statute to compile a list of the 200 most toxic substances found at Superfund sites. This list contains hazardous substances known to cause neurotoxic effects (e.g., toluene and others). ATSDR is also required to fill in any significant gaps in data on adverse health effects associated with exposure to these chemicals. For many of these chemicals, little is known about their neurotoxic

effects. ATSDR is collecting information on the neurotoxicity of these substances for dissemination to the public (4).

Another way that citizens may come into contact with solvents, pesticides, and metals is when one or more of these chemicals is spilled during transport. The acute and chronic neurotoxic effects in rescue workers and others who respond to spills and in citizens who do not have the time, knowledge, or ability to evacuate an area are not known. These situations can be serious because frequently there is a large concentration of the chemical in one location, the incident occurs suddenly, and the populations exposed may not know how to minimize adverse effects (4). Although ATSDR does not conduct or sponsor laboratory research in this area, it recently supported the National Academy of Sciences study *neurotoxicology and Models for Assessing Risk,* and was a cosponsor of the Third International Symposium on Neurobehavioral Methods in Occupational and Environmental Health.

National Institute for Occupational Safety and Health

NIOSH has identified neurotoxic disorders as one of the 10 leading occupational problems in the United States. NIOSH funds intramural and extramural activities designed to implement a program to identify, characterize, and control exposure to neurotoxic agents.

Intramural activities include an extensive surveillance program directed toward identification of a wide range of possible endpoints that may include, but are not restricted to or focused exclusively on, neurotoxic agents. These activities include the development of a database describing exposures from an extensive sampling of workplaces throughout the Nation, in order to identify patterns of use of known neurotoxicants, and a health hazard evaluation program that responds to requests for workplace assessments throughout the Nation (and which has identified cases of neurotoxic exposure in the past).

The identification and characterization of neurotoxic agents are conducted through both the intramural and extramural programs. Current intramural research includes the evaluation of possible long-latency effects of chronic exposure to ethylene and propylene oxide in primates and the effects of acute exposures to aliphatic carbons on motor activity and physiology of rodents. A human study is also being designed to evaluate the impact of exercise on exposure to combinations of chemicals. Effects of exposure will be assessed by means of behavioral measures and will be correlated with pharmacological information. A study of workers exposed to pesticides is in the early stages of development.

The primary thrust of NIOSH's intramural program is methods assessment. The Institute is participating in the National Health and Nutrition Survey, in which approximately 6,000 people from around the Nation will be given three tests from the Neurobehavioral Evaluation System (NES) in order to develop baseline data for future evaluations of exposure to neurotoxic chemicals. Similarly, NIOSH is one of three organizations conducting the international, cross-cultural assessment of the Neurobehavioral Core Test Battery (NCTB) recommended by the World Health Organization. The NCTB assessment has been conducted jointly with an evaluation of the NES. In this study, people in different age ranges were administered both batteries, thus providing information on the effects of participant age and means of administration. The NES is administered by a computer, and the NCTB is administered by a psychologist or other suitably trained professional (6).

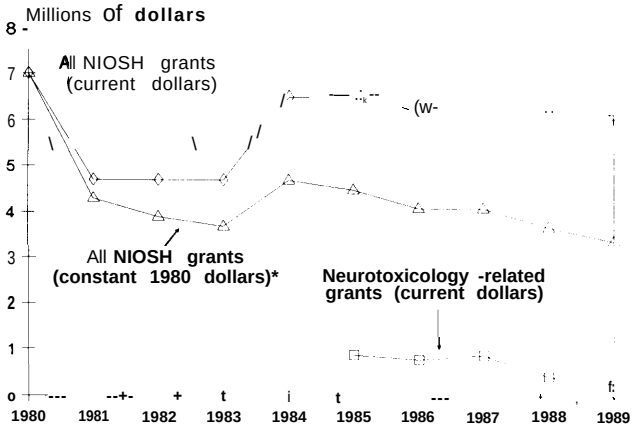
Funding for that portion of the intramural program directed exclusively at assessing neurotoxic disorders includes nine full-time-equivalent staff (including four persons with Ph.D.s) and $90,000 for the four projects currently funded.

Funding for neurotoxicology-related grants makes up a small portion of the total NIOSH extramural budget. In 1989, that total was $6.1 million, with $0.2 million (6), or less than 4 percent, devoted to neurotoxicology -related research. Since 1985, funding for neurotoxicology -related grants has declined, reflecting in part a decline in NIOSH's total extramural grants budget (figure 4-2). The current NIOSH budget has approximately half the buying power it did in 1980, due to inflation and budget cuts (47). NIOSH extramural grant programs are clearly weak in the neurotoxicology area.

Center for Environmental Health

Toxicology research at the Center for Environmental Health (CEH) in Atlanta, Georgia, is conducted under two divisions. The Division of Environmental Hazards and Health Effects is responsible for design, implementation, and analysis of expo-

Figure 4-2—Funding for NIOSH Research Grants



'Based on the Biomedical Research and Development Price Index
SOURCE: Office of Technology Assessment, 1990.

sure assessments and epidemiological studies. The Division of Environmental Health Laboratory Services develops and standardizes laboratory methods.

CEH is designing sensitive laboratory tests to assess the impact of toxic chemicals on public health. A major objective of its program is to develop tests that will enable investigators to evaluate toxic substances under a variety of biological conditions. Another major objective is to conduct tests at sites of environmental hazards to determine the threat to human health.

CEH conducts epidemiological investigations of human exposure to environmental hazards, including man-made and naturally occurring toxic substances, and determines the health effects resulting from exposure. It also provides emergency response to environmental disasters.

Department of Defense

The Department of Defense conducts and supports research related to neurotoxicity, much of which is relevant to the toxicity of chemical warfare agents. Defense-related neurotoxicology research programs were not evaluated by OTA for this report.

Department of Energy

The Department of Energy (DOE) supported only two research projects related to neurotoxicology through grants to public institutions in fiscal year 1988. Total funding of these projects was $487,000 (46). The first project examined the effects of environmental agents (as well as endogenous hormones and neurotransmitters) on cultured brain cells, A major goal of the project was to analyze the sensitivity of three major types of brain cells to environmental agents and to identify chemicals that influence the survival, proliferation, and differentiation of these cells.

The second project focused on the biological effects of magnetic fields. This type of non-ionizing radiation emanates from magnetic resonance imaging devices used in medicine and to a lesser extent from high-voltage power lines. There is considerable debate as to whether magnetic fields in the vicinity of high-voltage power lines adversely affect the nervous system. In this project, researchers have used several techniques to examine a series of physiological parameters, including possible effects on vision and other nervous system functions.

The Department of Energy Organization Act of 1977 mandates that DOE carry out the planning, coordination, support, and management of a balanced and comprehensive energy research and development program. The Act requires that DOE advance the goals of restoring, protecting, and enhancing environmental quality and assuring public health and safety (Public Law *93-577*, Title 42).

For several years, DOE supported applied research on the neurotoxicological and behavioral effects of chemicals. Recently, however, it changed the focus of some of its research programs from energy-related issues to fundamental biological questions, for example, sequencing the human genome. This shift in direction appears to have led to reductions in applied toxicological research, including work in the neurobehavioral field.

DOE research programs are currently not adequately addressing neurotoxicological concerns. DOE could be conducting neurotoxicological research into the health effects of energy-related processes and products including lead and lead substitutes in gasoline, methanol, and other fuels, and heavy metals used in nuclear and nonnuclear processes. It could be examining the effects of combustion products on the nervous system, and it could be working with Federal agencies and other public and private organizations to develop new and better toxicological tests to evaluate these effects.

Department of Agriculture

The U.S. Department of Agriculture (USDA) supports a small number of extramural research projects related to neurotoxicology. These projects are administered through the Cooperative State Research Service and fall into four major categories:

1. USDA competitive research grants,
2. special grants to State Agricultural Experiment Station scientists,
3. animal health funds, and
4. Hatch Act funds (34).

In fiscal year 1988, USDA supported 25 research projects related to neurotoxicology, nearly all of them involving insecticides and their metabolizes. Total funding for these projects was $422,000. Most of the research was supported by Hatch Act funds; the remainder was supported by special grants, animal health funds, and competitive grants. USDA research efforts span a wide range of objectives, from molecular biology and biochemistry, to structure-activity relationships, monitoring of agriculture workers, and the development of poisoning antidotes (21,33).

National Aeronautics and Space Administration

Toxicology research within the National Aeronautics and Space Administration (NASA) is conducted in the Biomedical Laboratories at the Johnson Space Flight Center in Houston, Texas. Space flight involves prolonged confinement in an artificial atmosphere with an array of equipment and materials. The Biomedical Laboratories evaluate spacecraft equipment and materials to ensure that flight crews are not exposed to harmful levels of toxic substances.

In the last several years, NASA has evaluated the neurobehavioral effects of many potentially toxic substances, including polyurethane thermal decomposition products, bromothifluoromethane, and various fire-extinguishing agents. In 1988, NASA completed a study of continuous low-dose exposure to Halon 1301, the active component in fire extinguishers in the space shuttle cabin.

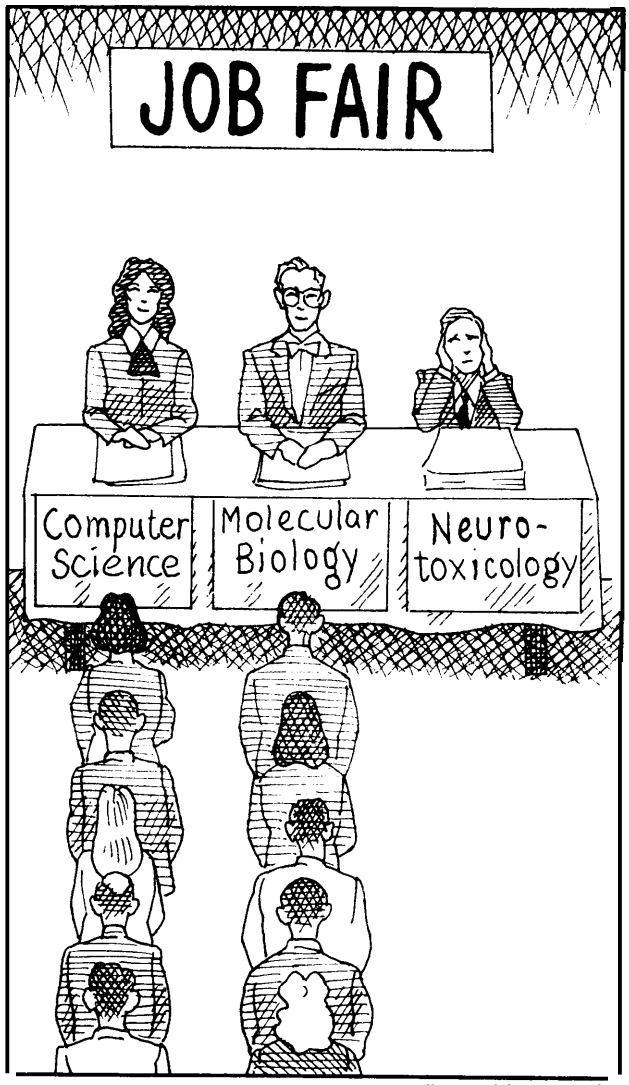
NASA has established maximum allowable concentrations (MACs) of atmospheric contaminants in manned spacecraft for missions of up to 7 days. These criteria are used in the development of all materials that will be used in space vehicles to ensure a nontoxic cabin atmosphere. In 1981, MACs were established or revised for some 200 chemicals that might be used in spacecraft.

ACADEMIC RESEARCH ACTIVITIES

Research interest in the neuroscience has increased rapidly in the last decade, as evidenced by growth in the membership of the Society for Neuroscience. The neurobehavioral sciences have made major advances in recent years, and society can continue to expect new and important discoveries that will not only improve understanding of the brain and behavior, but also make substantial contributions to public health. In the last decade, neurobehavioral toxicology has become an increasingly active field. Scientific papers are published in an array of journals, including two specialty journals *(Neurotoxicology and Neurotoxicology and Teratology).* A neurotoxicology specialty section has been organized within the Society of Toxicology, and two small scientific societies have been formed, the Behavioral Toxicology Society and the Behavioral Teratology Society. Behavioral scientists and neuroscientist have been appointed to the editorial review boards of the journals of the Society of Toxicology and participate in the peer review process of the extramural grants programs sponsored by NIH, ADAMHA, and EPA (48). However, despite recent advances, U.S. neurotoxicology research programs are small relative to the threat neurotoxic substances pose to public health.

Factors Influencing Academic Research Directions

Neurotoxicology will continue to benefit from the rapid advances being made in understanding the structure and function of the nervous system. With the tools of modern molecular biology and pharmacology, investigators are mapping and redefining the brain itself. As researchers learn more about the brain and its molecular components, they gain insights into how chemicals can alter nervous system structure and function. The detailed study of simple neuronal systems in invertebrates or in tissue culture can aid in understanding the mechanisms by which chemicals exert their effects in mammals; such studies should assist in screening for neurotoxicity. Improved understanding of the behavioral determinants of chemical actions will assist in the construction of test systems that will facilitate both



Illustrated by: Ray Driver

the detection and characterization of toxic effects. Increased efforts in academia, as well as in industry and government, are necessary in order to move beyond basic research and to apply basic knowledge to the development and validation of neurotoxicity tests.

The challenge in the years ahead will be to foster basic research and to persuade investigators and students that the field of neurotoxicology offers substantial opportunities for increasing our understanding of the structure and function of the nervous system. The neuroscience could provide novel and beneficial approaches to many important occupational and environmental health problems. These include identifying subtle neurological and psychiatric disorders occurring in exposed populations; exploring why some individuals appear to be particularly sensitive to chemicals; and developing preparations targeted at health problems associated with single chemicals, industries, occupations, modes of transportation, sources of energy, urban environments, and dietary habits. If occupational and environmental chemicals do play a key role in causing neurodegenerative disorders, for example, Parkinson's disease and Alzheimer's disease, prevention becomes an important goal.

The contributions of colleges, universities, and research institutes to neurotoxicology depend on continued grant support for research and graduate education. Neurotoxicology research and training take place in many university and medical center contexts, for example, departments of pharmacology, toxicology, pathology, psychology, neurology, psychiatry, anatomy, obstetrics and gynecology, ophthalmology, pediatrics, epidemiology, and occupational, environmental, preventive, and community medicine. There are only a few laboratories or institutes around the country that focus on neurotoxicology. There are no broadly based centers or departments of neurotoxicology. Thus, there are few environments in academia where neurotoxicology or behavioral toxicology is a major focus. As in any academic research environment, the spatial, financial, and personnel resources available, as well as the professional advancement and remuneration of the investigator, depend on the perceived merits of the research and on the interest and goodwill of the researcher's colleagues (48).

What leads an investigator to study a particular neurotoxic substance? In many cases, a chemical is of interest not because of its impact on human health, but because of its usefulness as a tool to study nervous system structure or function. Such studies provide necessary information about the substrates on which chemicals exert their effects and the mechanisms by which the effects occur. Knowing the mechanism of action of a toxic substance not only advances our knowledge, but aids in predicting what other chemicals will have similar effects. In other cases, a neurotoxic substance is selected for study because it has produced human injuries that have been well described or, if the compound has injured only a few people, because the injuries produced a severe impairment, repeatable in animals, that is of interest to the investigator, a funding agency, or public interest organization. There is also academic interest in understanding the possible role

of toxic chemicals in triggering neurodegenerative diseases.

Universities see basic research as one of their principal missions; routine toxicity evaluations are not usually considered to be an appropriate use of university resources or faculty time. There is little interest in studying either proprietary products or chemicals about which little or nothing is known unless the study offers insight into the mechanisms by which related chemicals exert known effects.

Funding pressures play a substantial role in an investigator's choice of research project. Two factors are at work: 1) the difficulty of finding a sponsoring agency, and 2) the short duration of typical grant awards. Neurotoxicology, like other emerging areas of toxicology, is a discipline that generates relatively small numbers of grant applications. Consequently, for the most part, there are no initial review groups, that is, expert committees appointed by Federal agencies to review the merits of neurotoxicology grant proposals. A study section charged with reviewing occupational or environmental health problems may understand the consequences of human exposure to a compound but not be able to review adequately the scientific methods of a research proposal or to balance its merit and relevance against those of other studies. If the proposal is forwarded to a study section that is competent to review the techniques involved, it may still face difficulties. A proposal deemed an appropriate application of existing techniques to an "applied" problem would not fare well in competition with a proposal that advances "basic" knowledge. One funding strategy that has been productive is to integrate neurotoxicity studies with a larger, multidisciplinary center or program project. In general, the success of any grant application depends largely on both accurate identification of the funding agency and specific tailoring of the proposal to the initial review group (48).

Funding usually extends for 3 to 5 years and takes the form of an individual grantor a multidisciplinary program project or center grant. Progress, as measured by publications, is necessary to maintain a research career. In order to achieve results rapidly, investigators are frequently drawn to compounds that produce easily recognized and reproducible effects after exposing animals for brief periods. Experiments involving agents that require inhalation exposure or chronic administration are more costly and require more effort, hence the number of journal articles produced at the end of the project is correspondingly reduced.

Cooperative Agreements Between Government and Academia

Government agencies sometimes channel intramural funds to 'investigators in universities or research institutes. These negotiated agreements tend to focus on projects of mutual interest and usually address specific problems. They have the advantage of permitting questions to be examined more rapidly and at less expense than would be possible intramurally. As a means of supporting extramural research programs, however, they have drawbacks: they often do not benefit from the intense scrutiny of the peer review process, and they tend to devalue research that does not produce data and conclusions in the short term. In times of tight budgets, this pattern of funding is the frost to be cut, because it is usually derived from the resources available to support intramural programs.

INDUSTRIAL RESEARCH ACTIVITIES

Industrial research falls into several categories and is funded by several mechanisms:

1. internal basic and applied research,
2. research conducted in contract laboratories,
3. research conducted through consortia,
4. contract research through universities, and
5. research grants for universities.

Toxicity evaluations conducted as part of internal applied research are necessary to develop safe and effective products, to protect employees, to protect the environment, and to control cost liability. Research programs vary considerably, depending on the types of products manufactured and economic considerations.

Pesticide Industry

The search for new pesticides begins with screening tests, which are designed to provoke a particular biological response. The toxicity profiles developed from screening tests may be considered to be proprietary information, because disclosure of them could give the competition information useful for product development. There are, however, methods

of giving outside experts data without compromising trade secrets.

Industry is willing to perform tests to obtain or maintain product registration, but it is cautious about devoting funds to the development of test protocols that might not satisfy regulatory authorities. Government and academic scientists may suggest testing strategies that they judge to be appropriate but may find it difficult to defend a specific testing scheme if there is an inadequate history of testing for the class of compounds in question or the extent of the public health hazard and possible economic impacts on society are difficult to predict (48).

Pharmaceutical Industry

Drug development begins with screening and development of structure-activity relationships. Acute and subchronic toxicity information emerges early in the process, but characterization of chronic toxicity usually develops more slowly. The quest for biological activity has produced some compounds that reach the market, but most are important research tools for the neuroscience and have no clinical utility or are too toxic to be used clinically.

Pharmaceutical industry research on toxic substances is directed largely toward therapy for central nervous system impairments and the development of animal models for screening drugs to ameliorate the signs and symptoms of nervous system damage. Examples of such injuries include oxygen starvation, MPTP-induced Parkinsonism, seizures induced by convulsant drugs, and brain injuries produced by excitotoxins (chemicals that produce so much activity in localized areas of the brain that the cells there die). The pharmaceutical industry also evaluates compounds in behaviorally normal animals and in the offspring of mothers exposed to toxic substances. It has promoted the development of a variety of neurotoxicity tests. The research contributions of the pharmaceutical industry emerge as a product nears approval. However, as is true in other sectors, much information generated by industry is never made public, even though it may be important in other contexts (48).

Consumer Product Industry

Information about the toxicity of consumer products typically emerges from premarket testing, human exposures, accidental ingestions by consumers, or in response to regulatory demand. Manufacturers of consumer products frequently maintain vigorous product development research teams. Their work sometimes produces serendipitous findings of wider interest, but it seldom sheds light on the possible neurotoxicity of their products.

Little information on the neurotoxicity of consumer products has been generated as a result of these recommendations. The laws administered by the Consumer Product Safety Commission (CPSC) permit the agency to require some toxicity evaluations as part of compliance with labeling and packaging regulations (15 U.S.C. 1261—Federal Hazardous Substances Act). For several years CPSC has encouraged regulated groups to develop voluntary standards. One such group is the art supplies industry, which developed recommendations for minimizing injuries through product labeling. (Some materials used by artists have neurotoxic potential.) Labeling standards may, in turn, prompt manufacturers to reformulate products in order to minimize toxicity and the need for warnings at the point of purchase. These recommendations were recently given the force of law in the Art Materials Labeling Act (Public Law 100-695).

Specialty and Commodity Chemical Industries

Chemical companies have a mixed record with respect to minimizing the adverse effects of chemicals on the health of their workers. Like other industries, however, they have no interest in marketing chemical products that may become substantial liabilities. Some companies rely on developing information of such high quality that it defines the state of the science—this is no doubt the best defense of a successful and prestigious corporation. To achieve this end, good scientists must be recruited and maintained as vigorous members of a corporate team. A good example is the publication by scientists at one major U.S. corporation of a series of high-quality papers describing the role of diketones in causing peripheral neuropathy (20). Unfortunately, less well capitalized companies cannot afford to invest in research of this kind, instead testing solely to comply with regulatory requirements. Commodity chemicals are produced by a number of different companies, so it is generally not in the interest of any one company to assume responsibility for evaluating the adverse health effects of a particular substance. The companies that manufacture and distribute such chemicals could be compelled to address the chemical's toxicity under

TSCA, or they could avoid such regulation by supporting a testing program under the auspices of a trade association.

INTERACTIONS AMONG GOVERNMENT, ACADEMIA, AND INDUSTRY

Industry and Government Consortia

Industry and government consortia devoted to environmental health are rare. One such consortium is the Health Effects Institute (HEI), an independent, nonprofit corporation ''organized and operated to study the health effects of emissions from motor vehicles . . .' (18). HEI serves as a potential model for other consortia. The institute makes no regulatory or social policy recommendations; its goal is "simply to gain acceptance by all parties of the data that may be. necessary for future regulations" (34). It has joined together the regulator and the regulated industry in mutual support of research activities targeted at joint concerns, and it does so by deriving funding jointly from EPA and the automobile industry.

The institute has recognized the importance of the effects of automobile emissions on the nervous system and on the quality of life in general. It has conducted a review of the topic (48) and has solicited research proposals in this area, The HEI model is a promising one for circumstances in which health concerns are generic and in which proprietary and competitive interests do not interfere with industry's participation.

Industry Research Consortia

The Chemical Industry Institute of Toxicology (CIIT) is a research institute funded by a consortium of chemical companies to study commodity chemicals of concern to members. CIIT has achieved a reputation for conducting excellent toxicological research targeted at a broad range of problems and has generated considerable goodwill in the process. Interest in neurotoxicity issues has recently been evidenced in the publications of the institute. However, in the absence of a significant new initiative, the contributions of this organization to knowledge of neurobehavioral effects may be limited.

CIIT could serve as a model for other industries with common interests, particularly industries meeting similar regulatory challenges. The pesticide industry as a group makes proprietary products, and it is unlikely that a group of competitors would be willing to share the cost of generating information about a single member's profit-making product. The companies are bound together by a common desire to be regulated appropriately and efficiently, however, and they could benefit from a joint research program that would help advance the state of the art in toxicology and risk assessment. This would include advances in the development of in vitro testing, the extrapolation of data from rodents to primates, the validation of screening approaches tailored to the needs of the pesticide industry, and the detailed characterization of identified toxicities and their mechanisms of actions, an important contribution to the risk assessment process.

Other industries with profitable products are challenged periodically by a rule-making activity or judicial finding requiring them to provide toxicity information. Such organizations might find it in their interest also to be part of a larger, standing organization with a governance structure that ensures that its research and testing of products are of the highest quality.

Cooperation in Epidemiological Investigations

Since individuals working in the chemical industry almost invariably experience higher levels of exposure to chemicals than do other groups in society, they are at greater risk of suffering the adverse effects of exposure to toxic substances. Thus, workers also serve as a sentinel population for the detection of neurotoxic disorders that occur in the general population. Often, workers are the first to identify adverse effects and bring them to the attention of their doctors. Epidemiological studies can be initiated by a number of organizations, but they are most often conducted by the CDC, ATSDR, and State health authorities. CERCLA and TSCA require manufacturers to collect and keep information regarding exposure and effects on health. Unions can play an important role in obtaining cooperation and in ensuring compliance with these efforts.

Unions can also help stimulate research activities pertinent to the health of their members. The United Auto Workers recently established jointly administered research programs with Ford, General Motors, and Chrysler in which studies of neurobehavioral

toxicity were identified as a priority. The funding was directed predominantly at human studies (26,49).

Charitable Organizations

The Third World Medical Research Foundation is a small, U.S.-based, nonprofit organization that encourages university and other biomedical scientists worldwide to find innovative solutions to toxic, nutritional, and other disorders of importance to developing countries. Working with university and NIH scientists, it was able to demonstrate the association of African cases of spasticity with infection by the HTLV-1 virus and to disprove a proposed causal association with methylmercury. More recently, it has focused on promoting the development of non-neurotoxic strains of the grass pea to prevent the spastic disease lathyrism and to generate safe, drought-resistant food and animal feed for drought-stricken areas of Africa and Asia.

EDUCATION

Education of Research Scientists

A significant portion of current knowledge about the effects of neurotoxic substances comes from basic research and the application of that research to environmental health problems. Yet many observers believe that there are too few scientists adequately trained in both neuroscience and toxicology. As discussed earlier in this chapter, research training exists in a variety of universities and medical centers, but there are few places in academia where neurotoxicology is a major focus.

The National Institute of Environmental Health Sciences awards grants to educational institutions for the training of environmental toxicologists. These grants support approximately 200 doctoral students in 24 universities. Only about half the schools offer intensive training in any aspect of neurotoxicology. Few institutions have comprehensive academic programs with adequate faculties to undertake a substantial research program. Since it takes about 5 years for a graduate student to earn a doctorate, fewer than 40 students supported by these training grants finish their degrees each year. Only some 10 to 15 students graduate from strong programs in neurotoxicology in the United States each year. While this does not mean that positions demanding an education in neurotoxicology will necessarily go unfilled—there are many other, usually small, programs that award the doctorate but do not have training grants-it does mean that the primary Federal program targeted to the Nation's manpower needs in toxicology can make only a small contribution in the area of neurotoxicology (23).

The NIEHS institutional training grants also support about 80 postdoctoral trainees, and another 5 students receive fellowships directly though individual training grants. Of course, many of these trainees come from predoctoral training programs in toxicology and thus represent no net gain in numbers. Since postdoctoral training takes a minimum of 2 years and only a fraction of the trainees stay in the field of neurotoxicology, this source yields only a small number of fully trained neurotoxicologists per year (23).

The American Board of Toxicology (ABT) certifies professionals in general toxicology. The certification examination includes neurotoxicology and clinical toxicology. More than 90 percent of the ABT-certified toxicologists possess a doctorate and have more than 3 years of professional experience. Questions about neurotoxicology and clinical toxicology are a routine part of the examination, including questions on the neurotoxicity of pesticides, the behavioral effects of metals, and neurotoxic drugs. Certification is for 5 years, and recertification includes continuing education and practice in toxicology (5).

Education of Health-Care Professionals

Much of the illness resulting from exposure to neurotoxic substances occurs among workers. Often, neurotoxic chemicals are first identified because of the occupational illness they have caused. Increased research and testing are needed so that harmful chemicals can be identified and worker exposure limited. Prevention of occupational illness is a challenging undertaking and involves identifying hazards, controlling hazards at the source, monitoring workers, and educating, training, and disseminating information to all persons involved. These topics have been addressed in a previous OTA report (45) and will not be covered in detail in this section. Instead, this discussion will be limited to the potential role that better education of health-care professionals might play.

Physicians, nurses, and industrial hygienists deliver most health care to workers who have been exposed to toxic substances in the workplace. The

number of professionals trained in the area of occupational health is not adequate to meet public health needs in the United States.

Physicians

A large percentage of physicians who provide occupational health services are employed by industry, yet many workers have no source of occupational health services and must rely on their family physicians. Family physicians are rarely trained in occupational medicine and thus are less likely to obtain histories of occupational exposure.

General training in occupational medicine during medical school is not extensive. Two surveys of medical schools, one conducted in 1977-78 (24) and the other in 1982-83 (25), found that the proportion of medical schools offering courses in occupational health in the preclinical years increased from 50 percent at the time of the first survey to 66 percent at the time of the second. The proportion of schools requiring that students take such courses increased from 30 percent to 54 percent. However, in those schools that required coursework in occupational health, there was a median curriculum time of only 4 hours over 4 years. A survey conducted by the Association of American Medical Colleges found that 70 percent of medical schools offer clinical electives in occupational medicine or environmental health. However, of the students responding to the survey (65 percent), only 1 percent actually took the offered elective (42).

Residency programs in primary care specialties—namely, family and general practice, pediatrics, internal medicine, obstetrics and gynecology, and psychiatry-rarely include training in occupational medicine. However, organizations such as the American College of Occupational Medicine, whose members are board-certified in occupational medicine, sponsor conferences and seminars to educate primary care and other physicians about occupational health issues (19).

Occupational medicine is one of the areas in which physicians specializing in preventive medicine can choose to be certified. The Institute of Medicine recently emphasized the need for a greater number of physicians specializing in occupational medicine. In 1987, there were 25 residency programs with 118 residents (0.1 percent of the total number of residents that year) (7). Between 1955 and April 1989, the American Board of Preventive Medicine certified 1,378 physicians in occupational medicine. The number of those physicians no longer practicing is not known (17). The requirements for board certification include 1 year of postgraduate training in preventive medicine; 1 year of residency in occupational health; 1 year of training, research, teaching, or practice of occupational medicine; and the completion of a master's degree in public health. The requirements are somewhat different for physicians who graduated from medical school before January 1984 (40).

Some effort to encourage medical students to enter the field of occupational medicine is being made. The American College of Occupational Medicine has a scholarship fund for medical students and residents interested in occupational medicine (41). Also, there is a mechanism under current law by which Congress could encourage the training of physicians in occupational health. Public Law 100-607 (sec. 613) states that:

> The Secretary [of the Department of Health and Human Services] may make grants to and enter into contracts with schools of medicine, osteopathy, and public health to meet the costs of projects (A) to plan and develop new residency training programs and to maintain or improve existing residency training programs in preventive medicine; and (B) to provide financial assistance to residency trainees enrolled in such programs.

Advocates of expanded training programs in occupational medicine note that the current language in the law says "may" and that changing the wording to "shall" would strengthen the law.

Nurses

Nurses provide a crucial aspect of care for workers exposed to toxic substances in the workplace. Indeed, they constitute the largest group of health professionals in the workplace-approximately 24,000 in 1980 (10). Occupational health nursing synthesizes principles from several disciplines in the health sciences, including, but not limited to, nursing, medicine, safety, industrial hygiene, toxicology, administration, and public health epidemiology. Activities focus on promotion, protection, maintenance, and restoration of health. The occupational health nurse is primarily concerned with the preventive approach to health care, which includes early detection of disease, health teaching, and counseling (2).

The American Board of Occupational Health Nurses is the only board that certifies nurses in occupational health. It has certified over 45,000 nurses since 1973 and estimates that 2,800 of them are still practicing (36). Certification requires a passing score on a national examination. Eligibility for the examination entails 5 years of experience in the specialty and a satisfactory record of formal and continuing education in designated subjects (3).

University-based baccalaureate programs in nursing provide courses and clinical experience in community and public health nursing and adult health that are basic to the practice of occupational health nursing. Specialty education in occupational health at the master's degree level is offered in several schools of nursing and public health. Although programs differ in their course requirements, most include adult health, elements of workplace exposures, epidemiology, toxicology, biostatistics, and opportunities for field work. Some programs provide education in neurotoxicology through courses, clinical experiences, and reviews of research (l). Doctoral-level education for nurses in occupational health has been offered for the past 10 years, and graduates are employed in the private sector as well as by governmental agencies and universities.

Federally supported programs for occupational health nurses have provided significant resources and continue to encourage training in this field. Since 1977, graduate-level academic programs have been funded as one component of the interdisciplinary Educational Resource Centers. These regional centers were developed under the Occupational Safety and Health Act of 1970 in response to the need for an adequate supply of trained professionals in occupational health (l).

The American Association of Occupational Health Nurses is the professional organization that represents registered nurses engaged in that specialty as practitioners, managers, consultants, and educators. The association develops standards of practice, monitors legislation related to occupational and environmental health, sponsors continuing education, and publishes a journal (l).

Industrial Hygienists

The role of the industrial hygienist is to recognize and reduce occupational health hazards in the workplace. Industrial hygienists thus attempt to anticipate, recognize, evaluate, and control those environmental factors or stresses stemming from the workplace that cause sickness, discomfort, or inefficiency among workers or members of the community (31). Industrial hygienists examine the overall safety of the working environment and recommend plant improvements. Part of their duty is to collect samples of dust, gases, liquids, vapors, and raw materials and determine the extent of worker exposure. For example, an industrial hygienist might sample the air inhaled by an employee working with organic solvents throughout an 8-hour shift (many organic solvents have potential or known neurotoxic properties, see ch. 10).

Most industrial hygienists have a bachelor's degree in engineering, physical science, biological science, or natural science, and some also obtain a master's degree in industrial hygiene. There are two levels of industrial hygienists, certified and uncertified. To become certified, one must complete a baccalaureate degree in the sciences or engineering, have 5 years of practical industrial hygiene experience, and pass a 2-day written examination given by the American Board of Industrial Hygiene. Hygienists may seek certification in the general field of industrial hygiene, or they may specialize in a number of areas, one of which is toxicology. Currently, there are approximately 4,000 certified industrial hygienists in the United States (35). Those hygienists who are uncertified rely on their skills, training, and experience but are not required to meet any minimum standards established by a governmental or professional organization (22).

The American Industrial Hygiene Association is a nonprofit professional society for persons practicing industrial hygiene in industry, government, labor, academic institutions, and independent organizations. The association, composed of some 7,400 members, publishes a journal and sponsors continuing education courses in industrial hygiene (15).

NIOSH Educational Resource Centers

Many of the professional organizations for toxicology, occupational medicine, occupational nursing, and occupational hygiene offer conferences and seminars as continuing education. The Federal Government also plays a role, through NIOSH's Educational Resource Centers, mentioned earlier. There are 14 centers located within universities throughout the United States. The centers conduct both ongoing research projects and programs offering academic degrees and continuing education. The

four main areas on which they focus are industrial hygiene, occupational medicine, occupational health nursing, and occupational safety. Courses are offered in toxicology and to a limited extent in neurotoxicology (1,47).

NIOSH also offers some in-house courses. None of these focuses on toxicology or neurotoxicology specifically, but some address the broader issues of occupational health and industrial hygiene.

SUMMARY AND CONCLUSIONS

Federal research related to neurotoxic substances is conducted primarily at the National Institutes of Health; the Alcohol, Drug Abuse, and Mental Health Administration; and the Environmental Protection Agency. Limited research programs are under way at the Food and Drug Administration, the Centers for Disease Control, the Department of Defense, the Department of Energy, the Department of Veterans' Affairs, the Department of Agriculture, and the National Aeronautics and Space Administration. Total Federal funding for neurotoxicology -related research (excluding research related to alcoholism and cigarette smoking) is $56.8 million. The bulk of this funding (85.2 percent) is through NIH and ADAMHA and tends to focus on the toxicity of drugs and the biochemical mechanisms underlying neurological and psychiatric disorders. A number of other Federal agencies and organizations provide limited funding for neurotoxicological research.

Research related to environmental neurotoxicology is confined primarily to the intramural program at EPA and the extramural program at the National Institute of Environmental Health Sciences within NIH.

The extent of academic research related to neurotoxicology is strongly dependent on the availability of grant support from the Federal Government. Academic research in neurotoxicology is supported almost exclusively by NIH and ADAMHA. Most extramural research funded by NIH is through the National Institute of Neurological Disorders and Stroke and the National Institute of Environmental Health Sciences, although several other Institutes have substantial programs. ADAMHA funds research through the National Institute on Drug Abuse and the National Institute of Mental Health.

EPA has a relatively large intramural neurotoxicology research program that has been limited in recent years by lack of funding for supplies and equipment. EPA has a small extramural grants program that has rarely funded neurotoxicology-related projects. Traditionally, Federal agencies have supported both intramural and extramural efforts to ensure a balanced, comprehensive, and cost-effective program.

FDA funds several research projects related to neurotoxicology, primarily through its intramural research programs. The National Center for Toxicological Research is conducting a number of intramura1 research projects related primarily to developmental neurotoxicology. The Center for Food Safety and Applied Nutrition has a small in-house program and is supporting three extramural research projects.

Within CDC, the National Institute for Occupational Safety and Health has small intramural and extramural programs devoted to the identification and control of neurotoxic substances in the workplace. CDC's Center for Environmental Health and Injury Control conducts epidemiological investigations of human exposure to environmental hazards.

Industry undertakes neurotoxicology-related research through several mechanisms, including in-house scientists, contract laboratories, consortia, contracts with universities, and grants to universities. Toxicity evaluations conducted as part of internal applied research are necessary to develop safe and effective products, to protect employees, to protect the environment, and to control liability costs. Research programs vary considerably, depending on the types of products manufactured and various economic considerations. Industry and government consortia, such as the Health Effects Institute, which studies the health effects of emissions from motor vehicles, are useful in bringing the regulated and the regulator together to support research projects of mutual interest.

The education of research scientists in neurotoxicology is limited, in part, by inadequate Federal support for training programs. Part of the difficulty in obtaining funding is due to the nature of neurotoxicology—the intersection of neuroscience and toxicology. Few academic departments devote significant resources to neurotoxicology, and few major Federal organizations devote their primary efforts to it. The National Institute of Environmental Health Sciences supports training in the neurotoxicology

field; however, funding limitations allow for support of only a relatively small number of trainees.

Millions of American workers are exposed to neurotoxic substances in the workplace, but illness stemming from these exposures often goes undetected and untreated. The subtlety of neurotoxic responses is one reason for this situation; for example, complaints of headache and nervousness are often ascribed to other causes. Another reason is the lack of adequately trained health-care professionals to diagnose and treat neurotoxic disorders. Medical schools, in general, devote little of their curricula to occupational health issues. After medical school, physicians may undertake residency training in occupational medicine, but in 1987 only about 1 in every 1,000 residents was specializing in occupational medicine. Nurses are also needed in the occupational health field to provide emergency services, monitor employee health, and provide counseling and referral to physicians. Industrial hygienists are needed to evaluate and control health hazards in the workplace.

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