## Chapter 3

# Fundamentals of neurotoxicology

‘ ‘The upsurge of interest in recent years in academia, industry, and government on the effects of toxic chemicals on the nervous system has created a new discipline of neurotoxicology.”

Peter S. Spencer, Ph.D.
Herbert H. Schaumburg, Ph.D.
***Experimental and Clinical neurotoxicology,*** 1980

. . . the recognition that a chemical component in street heroin [causes] Parkinson’s disease or [a] Parkinsonian disease or [a] Parkinsonian state comes like a lightning bolt to the medical community. . . . Now suddenly, with this new awareness, the neurological community is beginning to ask questions about other disorders, such as Lou Gehrig’s disease, Alzheimer’s disease. Could this possibly be the result of chemical exposure?

Bernard Weiss, Ph.D.
Testimony before the House Committee on Science and Technology
October 8, 1985

« . . . this is not a situation where we get depressed and anxious first and then developed these symptoms in *our* mind. This is a situation where these symptoms came along from exposure to fumes and chemicals and then we got severely depressed and anxious. ’

Aerospace Worker
Testimony before the Senate Committee on Environment and Public Works
July 15, 1989

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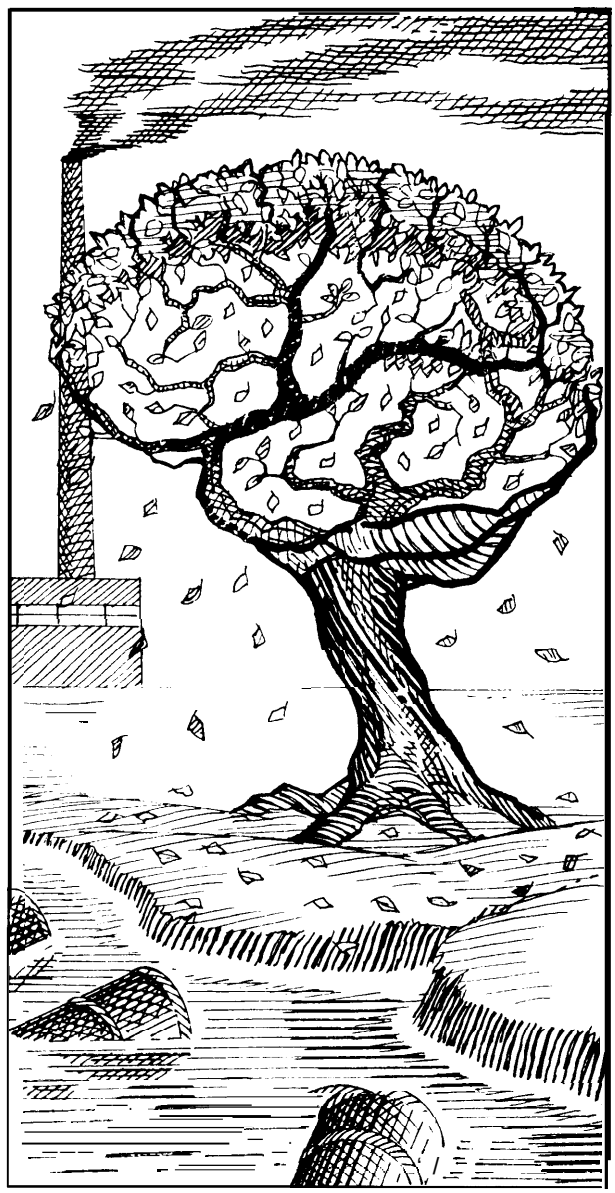
# Chapter 3
# Fundamentals of neurotoxicology

Toxicology is concerned with the adverse effects of natural or synthetic chemicals on the biochemical, physiological, and behavioral processes of living organisms. Because of the large number of chemicals in commerce and the wide variety of effects they may cause, toxicology is a broad science and toxicologists tend to specialize in one or more areas of the field. Biochemical toxicologists study the effects of toxic chemicals at the molecular and cellular levels. Regulatory toxicologists evaluate the risks posed by these substances and recommend actions that can be taken to reduce human exposure and environmental contamination. Clinical toxicologists examine the effects of drugs and toxic chemicals on human health and develop treatments to mitigate adverse effects. Behavioral toxicologists are concerned with the effects of toxic substances on animal and human behavior. Environmental toxicologists address the effects of pollutants on plants and animals, including humans (10).

neurotoxicology is concerned with the adverse effects of chemicals on the nervous system. Research in this field involves examining the modes by which neurotoxic substances enter the body, the effects of these substances on the various components of the nervous system, the biochemical and physiological mechanisms by which these effects occur, the prevention of damage to the nervous system, and the treatment of neurological and psychiatric disorders associated with exposure to toxic substances. Although scientists have made tremendous progress in understanding the nervous system, there is still much to learn about its function under both normal and abnormal circumstances.

## OVERVIEW OF TOXICOLOGICAL PRINCIPLES

In order for a toxic substance to cause adverse health effects, it, or its metabolic products, must enter the body and reach the target organ(s) at a sufficient concentration and for a sufficient length of time to produce a biological response. Chemicals differ in toxicity, with some being toxic in very small quantities and others having little effect at even very high doses. This relationship between exposure to a toxic substance and the extent of injury or illness resulting from it is called the "dose-response" relationship. In addition to dose, other critical variables determining toxicity are the properties of the chemical (e.g., its volubility), the means of exposure (through the lungs, stomach, or skin), the health and age of the exposed individual, and the susceptibility of the target organ or tissues (10).



*Illustrated by: Ray Driver*

### *Absorption, Distribution, Biotransformation, and Excretion*

Toxic substances normally enter the body through the lungs (inhalation), the skin (absorption), or the gastrointestinal tract (ingestion). In the industrial setting, most exposures occur through inhalation or absorption. After the substance enters the bloodstream, it is partitioned into body tissues, where it may act on target organs or tissues. For various reasons, including insolubility, some substances are not distributed through the body. Ultimately, toxic substances are eliminated from the bloodstream through accumulation in various sites in the body and through biotransformation and excretion.

Sites of accumulation of toxic substances mayor may not be the primary sites of toxic action. Carbon monoxide, for example, reaches its highest concentration in red blood cells, where it competes successfully with oxygen for binding sites in hemoglobin; it then causes widespread brain damage when these red blood cells fail to supply an adequate amount of oxygen to the brain. Lead, a potent neurotoxic substance, is found in highest concentrations in bone but exerts its most serious effects on the brain. The liver and kidney are major sites of accumulation of toxic substances, probably because of their large blood capacities and their roles in eliminating toxic substances from the body. Lipophilic toxic chemicals (i.e., chemicals soluble in fat-like materials; also termed hydrophobic) tend to accumulate in lipid-rich areas such as body fat. The brain may be particularly vulnerable to these toxic substances since 50 percent of the dry weight of the brain is lipid, compared to 6 to 20 percent of other organs of the body (5).

The body has a number of ways to detoxify foreign substances. The liver is the principal organ involved in detoxification, but other organs such as the kidney, the intestine, and the lung also play major roles. In fact, nearly every tissue tested has some capacity for detoxification; these capacities, however, are often limited to particular types of compounds. Adverse effects may occur when the quantity of the substance ingested overwhelms detoxification mechanisms, when an injury or illness has compromised the body's capabilities for detoxification, or when no mechanism is available to modify or remove the particular substance.

Before excretion, a substance may undergo biotransformation, the biochemical process by which it is converted into new chemical compounds which are often more easily excreted. This process usually changes lipophilic compounds to compounds which are more hydrophilic (water soluble) and therefore more easily excreted. Although biotransformation normally aids in the detoxification of substances, it sometimes results in compounds that are more toxic. Therefore, when analyzing neurotoxic substances and the health risks they pose, it is important to remember that the compound originally ingested or absorbed by an organism may not be the toxic substance that eventually acts on the nervous system.

Excretion of toxic chemicals from the body occurs through a variety of routes. Many substances are removed by the kidney and excreted through the urine. The liver is effective in detoxifying and removing substances that enter the body through the gastrointestinal tract. Some toxic substances, such as lead and mercury, are excreted from the liver into the bile and then into the small intestine, bypassing the blood and the kidneys (10).

Toxic substances are more easily removed from the body if they are hydrophilic or if they can be biotransformed into a more hydrophilic compound. Lipophilic toxic substances are removed from the body through a number of mechanisms; these include excretion in feces and bile, excretion of water-soluble metabolizes in the urine, expiration into the air, and excretion through the skin.

### *Interaction of Multiple Toxic Substances*

***The*** health effects of toxic substances are frequently examined with the assumption of a single chemical acting alone on a particular organ or type of tissue. Such an analysis has limitations, however. In some cases, an individual may be exposed to multiple chemicals that act on different organs and tissue types, and one cannot assume that the effect of these substances combined is the same as the combined effects of separate exposures. Chemical interactions may take place between substances. Sometimes the effects are additive (i.e., the combined effects are equal to the sum of the effects of each of the substances individually); at other times, the effects may be synergistic (i.e., the combined adverse effects exceed the sum of the individual effects).

A substance that is not toxic may increase the toxicity of another substance through a process called potentiation. More rarely, two toxic chemicals may result in no adverse effect when present together, a phenomenon called antagonism. Synergism, potentiation, and antagonism must be taken into account when examining exposure to complex mixtures of toxic substances such as those found in contaminated drinking water, smoke from an industrial fire, and fumes from a hazardous waste site (10).

## THE NERVOUS SYSTEM

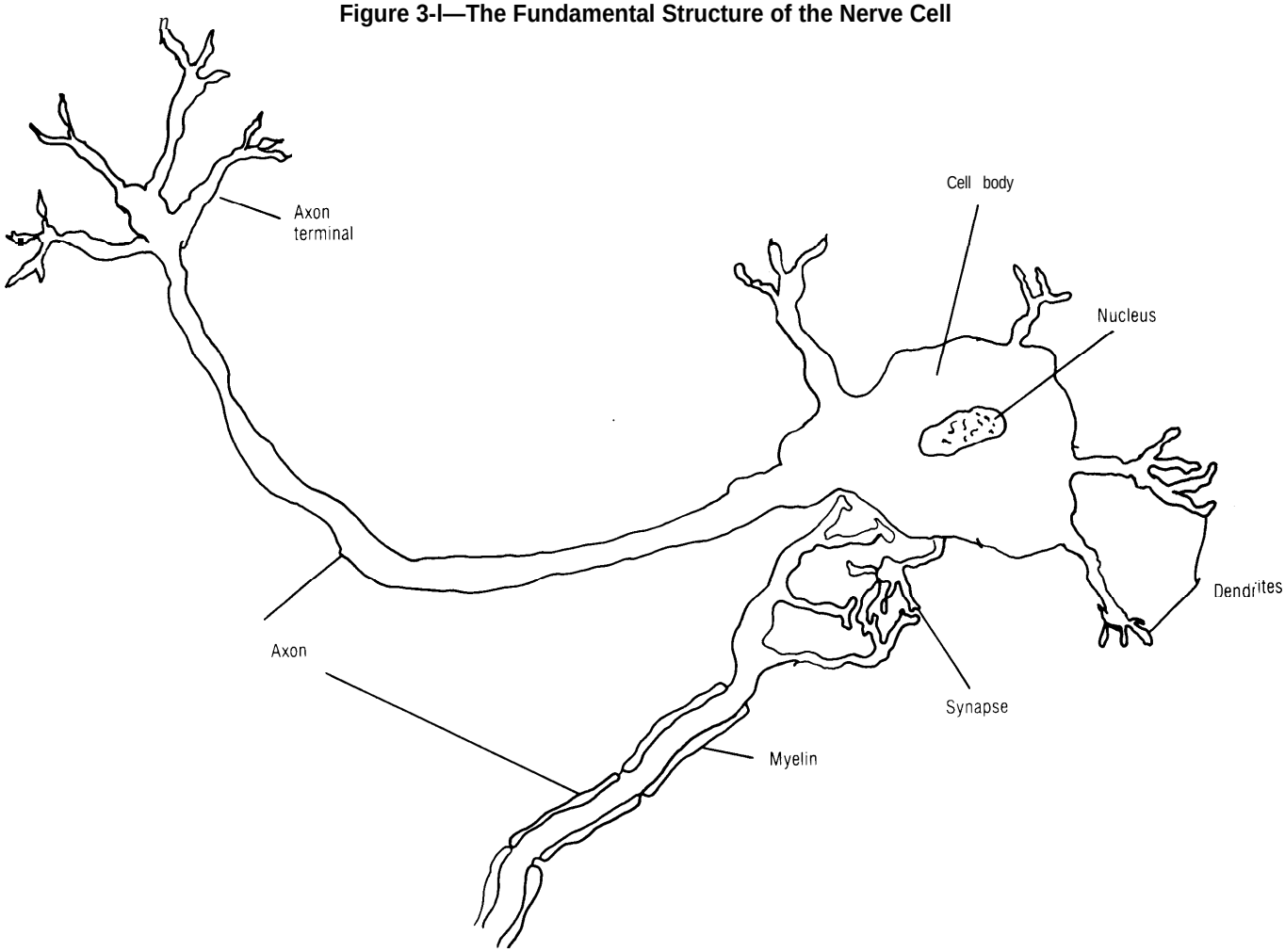
**The** fundamental unit of the nervous system is the nerve cell, or neuron (figure 3-l). While neurons have many of the same structures found in every cell of the body, they are unique in that they have axons and dendrites, extensions of the neuron along which nerve impulses travel, and in that they synthesize and secrete neurotransmitters, specialized chemical messengers that interact with receptors of other neurons in the communication process.

Certain nerve cells are specialized to respond to particular stimuli. For example, chemoreceptors in the mouth and nose send information about taste and smell to the brain. Cutaneous receptors in the skin are involved in the sensation of heat, cold, and touch. Similarly, the rods and cones of the eye sense light.

Glial cells appear to perform functions which support neurons-i. e., supplying nutrition, structural support, and insulation. Certain glial cells, for example, produce myelin, a fatty substance that covers the axons of many neurons throughout the body and acts as insulation.

Electrical information in the form of nerve impulses travels along the axons and dendrites of

**Figure 3-l—The Fundamental Structure of the Nerve Cell**



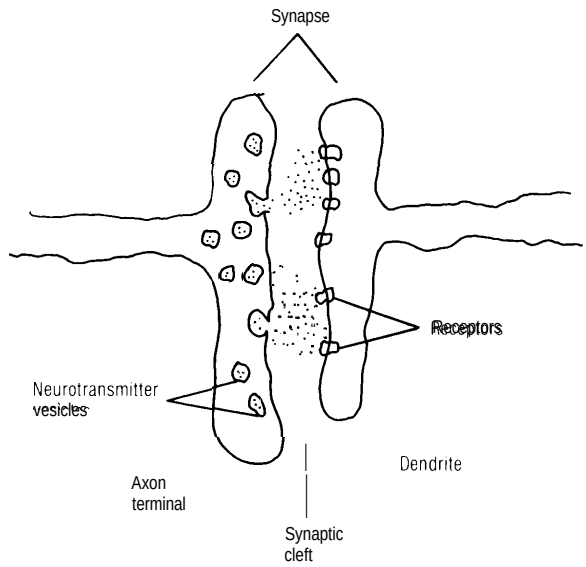

**SOURCE: Office of Technology Assessment, 1990.**

neurons. The impulses are generated by a rapidly changing flow of charged ions, primarily sodium and potassium, through channels in the nerve cell membrane. The insulating myelin sheath surrounding many nerves allows the electrical impulses (action potentials) to travel farther and faster than they otherwise could. Impulses generally travel away from the cell body of the neuron along axons and interact with the dendrites of other neurons. The point of interaction between adjacent nerve cells is called the synapse (figure 3-2). Here, neurotransmitters stored in vesicles in the axon terminal are released by electrical impulses, travel across the synaptic cleft, and bind to receptors on adjacent nerve cells, triggering biochemical events that lead to electrical excitation or inhibition. Information may also be transmitted from nerves to muscle fibers; in this case the point of interaction is called the neuromuscular junction.

Neurotransmitters are chemical messengers that can be subdivided into two categories: the classical neurotransmitters and the neuropeptides. Classical neurotransmitters include serotonin, dopamine, acetylcholine, and norepinephrine; the neuropeptides include endorphin, enkephalin, substance P, and vasopressin. Classical neurotransmitters are typically secreted by one neuron into the synaptic cleft, where they interact with receptors on the surface of the adjacent cell. Neuropeptides, on the other hand, may act over long distances, traveling through the bloodstream to receptors on other nerve cells or in other tissues. Binding of a transmitter to a receptor triggers a series of biochemical events that ultimately affect the electrical activity, or excitability, of the neuron. Depending on the type of transmitter released and the type of receptors, the effect of the chemical interaction is either to inhibit or to stimulate the electrical activity of the adjacent cell. When multiple neurons impinge on a single neuron, that neuron integrates the inputs, resulting in a net excitation or inhibition.

The nervous system is anatomically separated into two major divisions: the central nervous system and the peripheral nervous system. The central nervous system encompasses the brain and spinal cord, while the peripheral nervous system encompasses the nerves that travel to and from the spinal cord, sense organs, glands, blood vessels, and muscles.

**Figure 3-2-Chemical Communication at the Synapse**




**SOURCE: Office of Technology Assessment, 1990.**

The brain is composed of between 10 billion and 100 billion cells organized into vast networks of interacting axons and dendrites which comprise on the order of $10^{15}$ connections (17). The brain and spinal cord control vital functions of the body (including vision, hearing, speech, learning, memory, and muscular movements) through these complex networks and through a wide variety of neurotransmitters.

Information from sensory receptors is sent to the spinal cord and brain, where it is translated and integrated with other information. Sometimes the sensory information leads to muscular movement—for example, if one touches a hot stove. This reflex circuit involves both sensory neurons, which sense the heat and send the information to the spinal cord, and motor neurons, which send instructions to the muscles.

Most of the central nervous system is partially protected by the blood-brain barrier, a layer of tightly juxtaposed cells in blood vessel walls that allow some substances to pass from blood to neural tissue while keeping others out. This selective barrier protects much of the nervous system from substances that are either not necessary for metabolic functions or that may be damaging. Smaller compounds and compounds that are soluble in lipids tend to cross the barrier more easily, while larger compounds and substances which are soluble in water may be kept out. In addition, some compounds

cross the barrier with the help of carrier proteins which bind specifically to them. Drugs intended to act directly on the nervous system must therefore be designed in such a way as to pass through the blood-brain barrier into the brain. Most tranquilizers, narcotics, and anesthetics readily traverse the barrier.

### *Development and Aging*

***The*** first signs of the nervous system are exhibited around the 10th to 14th day of fetal development, when a flat sheet of around 125,000 cells forms from the outer layer of the ball of undifferentiated embryonic cells. The sheet then rolls into a tube, called the neural tube, which will eventually develop into the spinal cord and brain. Over the next 2 months these cells multiply, migrate, and begin differentiating into specific types of neurons and glia. The mechanism by which the undifferentiated embryo develops is unknown; however, embryologists believe that the cells' chemical environments play large roles in these determinations.

At approximately the 20th week, the neurons begin to extend axons and dendrites, initiating development of the nervous system's complex network of synaptic contacts. The nervous system is not fully developed until sometime during infancy. However, small modifications in the network do appear to take place even in the adult nervous system (7).

The nervous system undergoes major changes with aging. At the tissue and cellular level, the aging process results in nerve cell loss, neurofibrillary tangles (abnormal accumulation of certain filamentous proteins), and neuritic plaques (abnormal clusters of proteins and other substances near synapses). Neurons have a very limited capacity to regenerate; thus, as cells die, the complex neuronal circuitry of the brain becomes impaired. Aging is also accompanied by alterations in neurotransmitter concentration and the enzymes involved in the synthesis of these transmitters. Some neurons gradually lose their insulating myelin sheath, slowing conduction of electrical impulses along the axons.

Some-components of the nervous system appear to age differently than others. In a healthy person, for example, intellectual abilities such as memory, vocabulary retention, and comprehension seem to be maintained at least until the mid-70s, while motor skills, coordination, and sensory functions gradually become impaired (15). Specific areas of the brain may age at different rates. The locus ceruleus and the substantial nigra, two discrete areas of the brain, undergo a period of cell loss between the ages of 30 and 50, with the decline in cell number slowing thereafter (9). Between the ages of 20 and 80, the number of cells in the cerebral cortex may be reduced by half. In contrast, the Purkinje cells of the cerebellum decline in a linear fashion throughout life, while other clusters of cells are maintained at the same levels regardless of age.

## EFFECTS OF TOXIC SUBSTANCES ON THE NERVOUS SYSTEM

### *Structural Changes*

Toxic substances can alter both the structure and the function of cells. Structural alterations include changes in the morphology of the cell and the subcellular structures within it, and destruction of groups of cells. The long axons of some neurons, the inability of neurons to regenerate, and the nervous system's dependency on a delicate electrochemical balance for the proper communication of information make the system especially vulnerable to the effects of toxic chemicals.

When a toxic substance enters the human body, it can affect the biochemistry and physiology of neurons and glia in a variety of ways. The cells may swell, their internal contents may become more acidic, and biochemical processes such as protein synthesis and neurotransmitter secretion may be inhibited. Often these changes result from anoxia—i.e., oxygen deprivation. Neurons require relatively large quantities of oxygen because of their high metabolic rate and are therefore more vulnerable than other cells to anoxia.

At the morphological level, toxic substances seem to act selectively on the various components of the nervous system, damaging the neuronal bodies (neuropathy), axons (axonopathy), and myelin sheaths (myelinopathy). A common type of structural change induced by toxic substances on axons is central-peripheral distal axonopathy (CPDA). Degeneration of this type usually begins at the end of the axon and proceeds toward the cell body, hence it is often referred to as the "dying-back" process. Some organophosphorous insecticides can cause this type of damage after a single exposure; however, for the majority of chemicals producing this

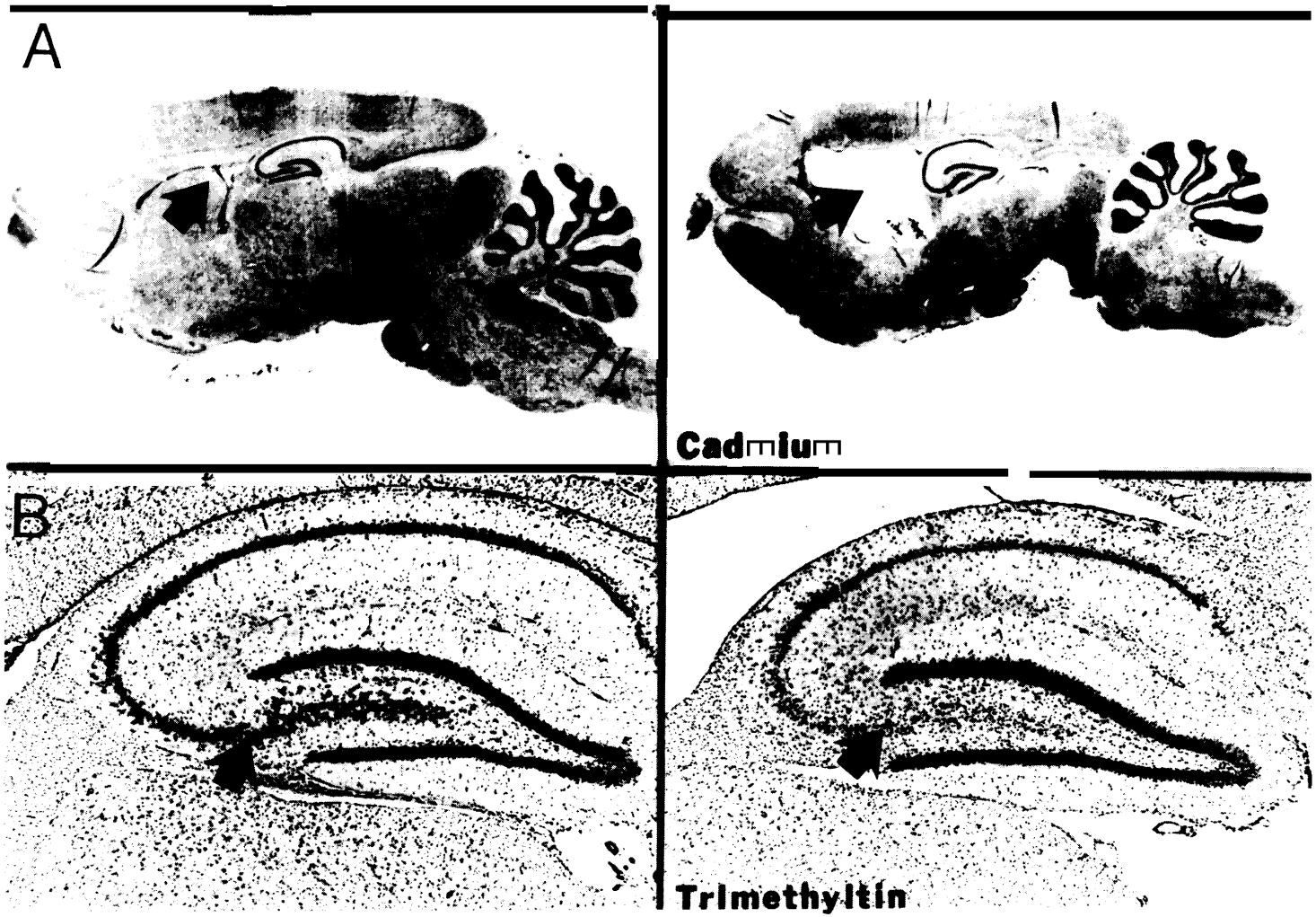



*Photo credit: J.P. O'Callaghan, U.S. Environmental Protection Agency*

Certain areas of the brain are more sensitive to toxic substances than others. A. Cadmium causes destruction of an entire region of the rat brain (neostriatum). B. Trimethyltin causes loss of a particular type of neuron (pyramidal cells) in the hippocampus, a region of the brain involved in the control of emotion, motivation, learning, and memory.

effect, continuous or prolonged intermittent exposure is necessary. Thousands of people were paralyzed during Prohibition after ingesting a popular alcohol substitute contaminated with an organophosphorous chemical (see box 3-A).

Toxic substances often cause a slow degeneration of the nerve cell body or axon that may result in permanent neuronal damage. Acute carbon monoxide poisoning, for example, can produce a delayed, progressive deterioration of portions of the nervous system that may lead to psychosis and death over a period of weeks (8).

### *Functional Changes*

Toxic chemicals can induce functional changes that involve modifications of motor and sensory activities, emotional states, and integrative capabilities such as learning and memory. Numerous sensory systems can be adversely affected, including sight, hearing, and touch and pain sensation. These effects may be caused by destruction of the myelin sheath that surrounds neurons (a process known as demyelination), damage to the neuron itself, or damage to the neurotransmitter system. Sensory changes are often reported as numbness or a tingling sensation. Methyl mercury is one chemical that is extremely toxic to the visual, sensory, and motor systems. Several episodes of large-scale human intoxication by this organic heavy metal have been described (3). In recent years, tests have been developed to detect sensory changes, particularly in visual and auditory functions resulting from exposure to toxic substances.

Organophosphorous and carbamate insecticides can induce functional changes by inhibiting acetylcholinesterase, an enzyme that breaks down the neurotransmitter acetylcholine. The functionalchanges include hyperactivity, neuromuscular paralysis, weakness, vomiting, diarrhea, and dizziness, with more severe cases exhibiting convulsions, coma, or death. The onset and duration of symptoms depend on the inherent toxicity of the insecticide, the dose, the route of exposure, and preexisting health conditions. Some organophosphorous pesticides can produce delayed and persistent neuropathy by damaging neurons in the spinal cord and peripheral nervous

### *Box 3-A—The Ginger-Jake Syndrome*

During Prohibition, contamination of a popular ginger extract with triorthocresyl phosphate led to an epidemic of partial paralysis that came to be known as the Ginger-Jake syndrome. The case serves as a dramatic example of the neurotoxic potential of organophosphorous substances.

Extract from the Jamaica ginger had been used in the United States since the 1860s as a medicinal tonic. A typical preparation contained 70 to 80 percent alcohol by weight and reputedly aided in digestion, prevented respiratory infections, and promoted menstrual flow. Nicknamed ''Jake," *the* tonic became especially popular in the early 1900s in areas where local legislation outlawed the sale of alcoholic beverages.

During Prohibition, the legal sale of ginger extract was limited to a "fluidextract" which contained 5 grams of ginger per cubic centimeter of alcohol (usually ethanol). Since the high concentration of ginger yielded a solution too irritating to drink, the requirement was supposed to confine its use to medicinal purposes. Department of Agriculture agents would occasionally check for the appropriate ginger content by boiling off the alcohol and weighing the solid residue. However, bootleggers soon saw the possibility of dissolving small amounts of ginger into alcohol and substituting adulterants, such as molasses or castor oil, for the remaining required solid content. The result was a potable alcohol source that could be sold at bargain prices.

In 1930, perhaps in response to an increase in the price of castor oil, one bootlegger tried Lyndol, a heat-resistant oily material used in lacquers and varnishes, as an adulterant. When consumed, the triorthocresyl phosphate in Lyndol caused axonal degeneration in neurons of the central and peripheral nervous systems. Depending on the severity of the case, symptoms ranged from temporary numbness and tingling in the extremities to permanent partial paralysis. Estimates vary widely, but between 20,000 and 100,000 people were permanently affected before all the poisonous shipments were seized.

SOURCES: M.B. Abou-Doniaand D.M. Lapadula, "Mechanisms of Organophosphorus Ester-Induced Delayed neurotoxicity: Type I and Type II, " *Annual Review of Pharmacology and Toxicology* 30:405-440, *1990;* S.D. Davis and R.J. Richardson, ''Organophosphorus Compounds, " *Experimental and Clinical Neurotoxicology*, P.S. Spencer and H.H. Schaumburg (eds.) (Baltimore, MD: Williams & Wilkins, 1980); J.P. Morgan, "The Jamaica Ginger Paralysis," *Journal of the American Medical Association* 248: 1864-1867, 1982; J.P. Morgan, City University of New York, personal communication, Jan. 4, 1990.

system; in these cases, the resulting muscle weakness may progress to paralysis (4, 26).

Motor and sensory functions are closely linked within the nervous system. Body movements, for example, involve complex feedback interactions between motor and sensory neurons to allow smooth, controlled movements. Consequently, damage to sensory systems can indirectly affect certain motor functions. Some toxic substances affect motor neurons directly; others damage both sensory and motor neurons (a condition termed mixed neuropathy). Neurophysiological tests are available to monitor the conduction velocity of impulses along nerve axons, and various neurological tests can be used to detect muscle weakness and lack of control of muscular movements.

Toxic substances often affect the higher functions of the nervous system such as learning, memory, and mood. Exposure to inorganic lead can lead to mental retardation in children; at lower levels of exposure, however, it may manifest itself as a shortened attention span or a learning disability (16, 23). Various tests are available to detect impairment of these processes, some of which are described in chapter 5.

### *Behavioral Effects*

Behavioral changes may be the first indications of damage to the nervous system. An individual exposed to a toxic substance may initially experience vague feelings of anxiety or nervousness. These feelings may progress to depression, difficulty in sleeping, memory loss (see box 3-B), confusion, loss of appetite, or speech impairment. In severe cases, a person may exhibit bizarre behavior, delirium, hallucinations, convulsions, or even death. Often, behavioral toxicological testing can detect an impairment for which investigators have not yet found a physiological or biochemical mechanism.

Exposure to neurotoxic chemicals during pregnancy may not produce obvious symptoms of behavioral toxicity until long after the exposure has ceased. This phenomenon has given rise to the field of behavioral teratology (18). An issue of particular concern to neurotoxicologists is the latency of some neurotoxic effects. One explanation for latent, or "silent," damage is that at younger ages the brain may be able to compensate for some adverse effects. With age, this ability to compensate diminishes, and the damage inflicted early in life may become apparent (19, 25). It has been proposed that exposure to toxic substances may trigger biochemical events that may later contribute to the cause of certain neurological diseases such as Parkinson's disease, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), or Alzheimer's disease. This hypothesis, sometimes referred to as the environmental hypothesis, has recently been the subject of increased interest following the MPTP incident (see box 3-C) and the Guam-ALS episode (19). (See ch. 2).

### *Susceptibility to neurotoxic Substances*

Everyone is susceptible to the adverse effects of neurotoxic substances, but individuals in certain age groups and persons with certain health problems may be particularly at risk. The developing nervous system is especially vulnerable to certain toxic substances. Its cells are actively growing, dividing, migrating, and making synaptic connections, and the blood-brain barrier is not yet fully developed. During the first weeks of prenatal development, toxic substances may interrupt closure of the neural tube, leading to such birth defects as spina bifida (a defect in which the vertebral column is exposed) and anencephaly (the absence of all or part of the brain). During later development, the risks of exposure have diminished for many components of the nervous system; however, the cerebrum and cerebellum, major portions of the brain responsible for functions such as sight and movement, remain particularly vulnerable (15, 22).

Factors such as dose of the toxic substance and nutritional deficiencies in the mother also influence the extent of damage. Ethanol (alcohol), cocaine, antibiotics, and steroids, for example, can all adversely affect the fetal nervous system (18). Since few drugs have been adequately evaluated for effects on the developing fetus, physicians are advised to exert special care in prescribing drugs to pregnant women.

As the structure and function of the nervous system decline with age, individuals become more susceptible to the effects of many neurotoxic substances. Adverse effects that might have been masked at a younger age by a vital, healthy nervous system may become apparent. Those suffering from neurological disorders are at greater risk because toxic chemicals may exacerbate existing problems. Persons suffering from multiple sclerosis or neuromuscular disorders, for example, are vulnerable

### *Box 3-B—The Endangered Hippocampus*

Deep inside the brain is a crescent-shaped structure that acts as a switching and information storage center. The hippocampus, as it is called, is a site of convergence of many neural pathways and is in a strategic position to modulate chemical information as it is transferred from one region of the brain to another, It is a major component of the limbic system, which, along with the hypothalamus and amygdala, is involved in the control of emotion and motivation. In recent years, evidence has mounted that the hippocampus is important if not critical, to learning and memory processes. These processes are significantly impaired if the hippocampus or certain nerve pathways entering it or leaving it are destroyed.

Learning and memory are often adversely affected by toxic substances, and some researched believe that the hippocampus is an important target site of these substances. A number of toxic chemicals preferentially affect the hippocampus, including many metals, some abused drugs, and certain viruses (including those responsible for rabies and AIDS). The hippocampus is also adversely affected in neurodegenerative disorders such as Alzheimer's disease and in Down's syndrome.

Many of the cells of the hippocampus appear to use the excitatory amino acids glutamate and aspartate as neurotransmitters, Under normal circumstances the synthesis, storage, and release of these transmitters is delicately balanced. However, adverse conditions associated with trauma, stroke, or exposure to toxic chemicals and drugs may upset this balance, sometimes leading to an event known as **excitotoxicity. This is** a process by which excitatory neurotransmitters released from neurons flood neighboring cells and weaken their membranes, leading to cell death. The mechanism of this cascade of events is being examined closely in the case of glutamate because the characteristics of the receptor that binds this transmitter are beginning to be understood. Recently, it was discovered that the drug PCP blocks glutamate receptors and that other compounds that effectively block this receptor are virtually identical to PCP.

There is much to learn about the transmitter systems in the hippocampus and the mechanisms by which toxic substances alter these systems. Clues to how some aspects of learning and memory are altered by toxic substances may ultimately be found in the biochemical machinery of this region of the brain.

SOURCES: S. Blakeslee, 'Pervasive Chemical, Crucial to the Body, Is Indicted as an Agent in Brain Damage," New York *Times, Nov. 29, 1988;* TJ. Walsh and D.F. Emerich, "The Hippocampus as a Common Target of neurotoxic Agents," *Toxicology 49:137-140, 1988.*

because the neural targets of these diseases are the same as those of many neurotoxic substances. Persons suffering from mental disorders may also be more susceptible to neurotoxic substances because of possible augmentation of their symptoms. Toxic chemicals can cause or exacerbate anxiety, depression, mania, and psychosis. Most adverse effects are short-term and reversible; however, long-term effects, including permanent damage to mental health, can occur.

Diseases involving organs such as the kidney or liver can indirectly affect the nervous system. The build-up of waste products in the bloodstream due to kidney failure or diabetes, for example, can cause adverse effects on nervous tissue similar to those caused by environmental exposure to toxic chemicals.

Malnourished individuals are generally at greater risk of harm from neurotoxic substances than are individuals with adequate diets. A person with a thiamine (vitamin $B_1$) deficiency, for example, is more susceptible to the toxic effects of ethanol on the liver (15). This problem is especially relevant for developing nations-that face regular food shortages.

## CLASSES OF neurotoxic SUBSTANCES

neurotoxic substances can be categorized according to the structural or functional changes they cause. The following categorization, which groups neurotoxic substances according to where they appear to act, is a summary of a scheme developed by Spencer and Schaumburg (20). The scheme includes the following targets: neurons, glial cells and myelin, the neurotransmitter system, and blood vessels supplying the nervous system.

Some adverse effects may not be included in this approach. For example, neurotoxic substances may also affect cells of the immune system, which can in turn influence nervous system function at any of these neural sites. Interactions between the immune and nervous systems have become the subject of

### *Box 3-C-MPTP and Parkinson's Disease*

In recent years, the hypothesis that Parkinson's disease and other neurological disorders might be triggered by environmental factors has become more widely accepted. Although toxic substances have long been considered possible contributors to the cause of some disorders of the nervous system, the MPTP incident has focused more attention on this environmental hypothesis.

MPTP is the abbreviation for l-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine, a compound that can be created during the production of synthetic heroin. Remarkably, in just 5 to 15 days, this highly neurotoxic substance can induce a syndrome virtually identical to Parkinson's disease—a disease that usually occurs late in life and develops slowly over a period of years. Both Parkinson's disease and the MPTP-induced syndrome are characterized by tremors and lack of muscular control that stem from degeneration of neurons in the substantial nigra, a region deep in the central area of the brain. Neurons in the substantial nigra synthesize and secrete the neurotransmitter dopamine, hence Parkinson's patients are treated with levodopa, a precursor of this neurotransmitter.

The discovery of the link between MPTP and Parkinson's disease has dramatically changed the nature of research on this disease. Much work has focused on $MPP^+$, a metabolize of MPTP that is responsible for the adverse effects on the brain. Recently, researchers discovered that a monoamine oxidase inhibitor, a type of drug sometimes used to treat depression, blocks the conversion of MPTP to $MPP^+$. Other researchers have shown that the monoamine oxidase inhibitor Deprenyl, administered to Parkinson's patients in combination with levodopa, reduces the symptoms of the disease and extends their lives. It was found that Deprenyl slows the rate of degeneration of neurons in the substantial nigra, perhaps making it useful in the treatment of Parkinson's disease.

The MPTP story illustrates how a neurotoxic substance might cause or contribute to the development of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. The relative contributions of environmental and genetic factors to the causes of these diseases are not understood and are the subject of considerable research and debate within the scientific community. Although the extent to which a neurotoxic substance contributes to the cause of Parkinson's disease is unclear, the MPTP story serves as an example of how neurotoxicological research can lead to a better understanding of the causes of neurological disease and ways to treat it.

SOURCES: LJ. Kopin and S.P. Markey, "MPTP Toxicity: Implications for Research in Parkinson's Disease,' *Annual Review of* Neuroscience 11:81-96, 1988; J.W. Langston, P. Batlard, J.W. Tetrud, et al., "Chronic Parkinsonism in Humans Due to a Product of Meperidine-Analog Synthesis," *Science* 219:979-980, 1983; R. Lewin, "Big First Scored With Nerve Diseases," *Science* 245:467-468, *1989.*

considerable interest in recent years, leading to a new field of research known as neuroimmunology.

### *Actions on the Neuronal Membrane*

As described earlier, the neuron consists of the cell body and the dendrites and axons projecting from it. The neuronal membrane contains a complex system of pumps, receptors, and channels through which charged molecules (ions such as sodium, calcium, and potassium) travel into and out of the cell. Toxic substances may act on any of these components. Determining the mechanism of action of neurotoxic substances often requires researchers to investigate possible adverse effects on a variety of receptors and channels.

Naturally occurring toxic substances such as tetrodotoxin (from the puffer fish) and saxitoxin (from the marine alga responsible for paralytic shellfish poisoning) block ion channels, initially causing numbness in the face, neck, and limbs. This is followed by difficulty in speaking and swallowing and by an inability to coordinate muscular movements. In severe cases, respiratory paralysis may result.

Toxic substances can also act to increase the flow of ions across the membrane, resulting in many of the same symptoms as those caused by the channel blockers. Scorpion toxin and the pesticide DDT, for example, act by increasing the flow of sodium ions. Pyrethroid pesticides are an example of widely used commercial compounds that exert toxic effects in this manner.

### *Actions on Neuronal Structures*

Substances such as mercury and lead cause degeneration of the central nervous system. Intoxication by organic mercury, particularly in children, can cause degeneration of neurons in the cerebellum

*Photo credit: U.S. Environmental Protection Agency*

and can lead to tremors, difficulty in walking, visual impairment, and even blindness. Lead adversely affects the cortex of the immature brain, causing irreversible mental retardation in young children (23).

The peripheral nervous system is particularly vulnerable to the effects of toxic substances because it lies outside the central nervous system which is partially protected by the blood-brain barrier. The antitumor agent doxorubicin, for example, causes degeneration of both central and peripheral nerve axons (21).

Degeneration of the axon is one of the most frequently encountered neurotoxic effects. Many chemicals and drugs will cause axonopathy but will not affect the cell body. In most cases, repeated or chronic exposure is required before adverse effects occur. The precise mechanisms by which axonal degeneration occurs are not understood. Some research suggests that toxic substances block the transport of substances between the cell body and regions of the axon.

Often, degeneration begins at or near the end of the axon and proceeds toward the cell body. As noted earlier, this type of pathological effect is called central-peripheral distal axonopathy (CPDA). An afflicted individual may experience loss of sensation in the hands and feet or muscular weakness. In some cases, the effects gradually worsen, and the loss of sensation progressively ascends to the limbs as shorter nerves become affected. With time and removal from exposure, recovery is often possible.

Numerous toxic substances cause CPDA, including such industrial chemicals as carbon disulfide (discussed further in ch. 10), hexane, acrylamide, and Lucel-7 (discussed in ch. 2). Drugs that cause this axonopathy include thalidomide (whose other tragic side-effects on the developing fetus have been well documented) and vincristine, a drug used to treat cancer. Alcohol abuse, some organophosphorous pesticides, and natural toxins present in buck-

thorn (from the fruit of the shrub *Karwinskia humboldtiana) also* adversely affect the nervous system in this manner.

A less common form of axonal degeneration, central-distal axonopathy, is characterized by adverse effects on the spinal cord but not on the peripheral nervous system. Some 10,000 cases occurred in Japan between 1956 and 1972, when the drug clioquinol was considered a safe and effective nonprescription treatment for diarrhea caused by an amoeba. Affected individuals experienced abdominal discomfort, numbness in the feet, weakness in the legs, blurred vision, and, in cases where large amounts of the drug were consumed, encephalitis (inflammation of the brain).

The most serious form of neurotoxicity involves the complete loss of nerve cells. Sensory nerve cells may be lost in patients treated with megavitamin doses of vitamin $B_6$; hippocampal neurons undergo degeneration with trimethyltin poisoning; motor nerve cells are affected in cycad toxicity, which has been linked tentatively to Guam-ALS-Parkinsonism dementia (19).

### *Actions on Glial Cells and Myelin*

A large number of neurotoxic substances can cause degeneration of glia1 cells and the myelin that these cells produce. Diphtheria toxin, for example, interferes with the cell bodies of myelin-producing glial cells. Hexachlorophene interferes with the energy-producing mitochondria within glial cells. Perhexilline maleate, a drug used to treat the chest pain of angina pectoris, sometimes causes degeneration of myelin and leads to numbness in the hands and feet and muscle weakness.

### *Actions on the Neurotransmitter System*

Other toxic substances may affect the neurotransmitter systems of neurons. The nicotine in cigarettes and some insecticides, for example, mimic the effects of the neurotransmitter acetylcholine. Organophosphorous compounds, carbamate insecticides, and nerve gases act by inhibiting acetylcholinesterase, the enzyme that inactivates the neurotransmitter acetylcholine. This results in a build-up of acetylcholine and can lead to loss of appetite, anxiety, muscle twitching, and paralysis.

Amphetamines stimulate the nervous system by causing the release of the neurotransmitters norepinephrine and dopamine from nerve cells. Cocaine affects both the release and reuptake (the process by which neurotransmitters and their metabolizes are recycled) of norepinephrine and dopamine. Both amphetamines and cocaine can cause paranoia, hyperactivity, and aggression, as well as high blood pressure and abnormal heart rhythms.

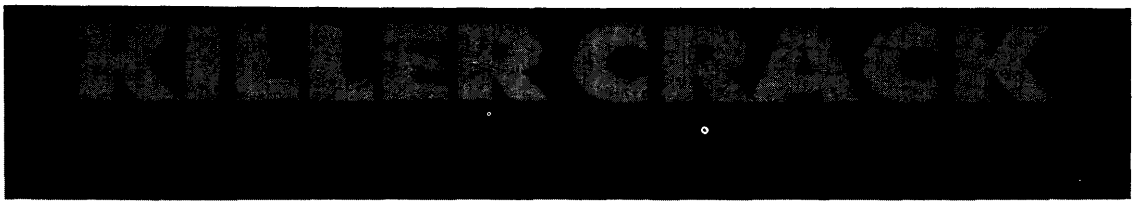
Some drugs act by altering the action of the neurotransmitter serotonin. LSD, a drug widely abused in the United States, especially in the 1960s, is a potent hallucinogen. Although it is not known precisely how LSD functions, it does interfere with the activity of the neurotransmitter serotonin. Mescaline and psilocybin (from the hallucinogenic mushroom Psilocybes) act in a similar fashion.

Opium-related drugs such as morphine and heroin act at specific opioid receptors in the brain. These receptors interact with the endogenous brain neuropeptides, such as the enkephalins and endorphins, which control the perception of pain and give rise to feelings of euphoria. Consequently, drugs acting at opioid receptors cause sedation and euphoria and reduce pain. They also tend to slow the heart rate and may cause nausea, convulsions, and slow breathing patterns. They are highly addictive, leading to as yet unidentified changes in the structure and function of the nervous system. Researchers are actively seeking to understand the mechanisms by which addiction to opiates occurs. Withdrawal from this class of drugs leads to impaired vision, restlessness, and tremors.

A relatively recent phenomenon of increasing concern to health-care workers is the addicted infants born to women who use drugs such as cocaine. These infants suffer from a variety of behavioral abnormalities. Many of the symptoms of withdrawal seen in adults can also be seen in these infants immediately after birth (see box 2-B).

### *Actions on Blood Vessels Supplying the Nervous System*

The nervous system is supplied by an extensive system of blood vessels and capillaries. The brain needs large quantities of oxygen and nutrients and relies on an extensive circulatory system to supply needed substances and to remove toxic waste products. Lead damages capillaries in the brain and leads to the swelling characteristic of encephalopathy. Other metals (e.g., cadmium, thallium, and mercury) and organotins (e.g., trimethyltin) cause




### Crack is Cocaine

Crack is not a new drug—it's actually freebase cocaine. It's different because:

- Of the way it's made
- It's pre-packaged for users, and
- It's much stronger and deadlier than other types of cocaine.

Crack is sold in smokable chips or tiny rocks. Sometimes it's in foil or plastic bags or tiny plastic vials—little bottles with colored stoppers like the kind used for perfume.

Dealers love crack—they get rich quickly. Crack is easy to handle and highly addictive. This guarantees steady customers. Crack is a dealer's dream. But it's a user's nightmare because it's quickly and highly addictive, even after a few doses.

### Crack Only Looks Harmless

Crack looks like grey or white-colored soap, small rocks or little pellets. Some people say it's odorless, but others think it has the pungent, bitter aroma of burning rubber, where the drug is often used.

Crack appears to be a cheap and easy way to get high. It's usually smoked in water pipes or cigarettes. But the act of smoking doesn't seem as dangerous as injecting something up the nose or inhaling powder into the lungs. But users seriously fool themselves if they think so.

Some heroin addicts have turned to crack because they fear the spread of AIDS among needle users. Crack has not yet been done many of them learn quickly to their sorrow.

Other addicts have turned to crack because they think it is safer than other methods of freebasing, albeit not much safer.

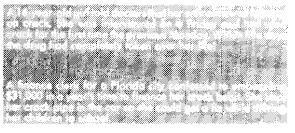
### High Cost

The crack high is cheap—at the start. The first dose only costs as little as $5. This makes it especially attractive to young people. They also like crack because it is not bulky or expensive and small sale. The dealer has no need for a white-collar connection. Drug experts say the habit will cost hundreds of dollars a week.

### Deadly Cycle

Crack triggers an explosive, short-lasting euphoria. It rushes the brain's supply of several essential neurotransmitters and affects the body in many harmful ways. Many users try to feed the craving by using more and more of the drug, but each dose produces a shorter high. Crack is a powerful addictive drug that can cause seizures, heart failure, respiratory arrest, stroke, and death.

### I n s Addiction



### Physical Effects

Physical effects [illegible] can be tragic. For younger users as well as older users, crack can cause many dangerous changes in blood pressure, heartbeat, and breathing. It can cripple or kill in many ways.

- [illegible]
- [illegible]
- [illegible]
- [illegible]

### Psychological Effects

[illegible]

### Tragedy

[illegible]

Users Say:

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

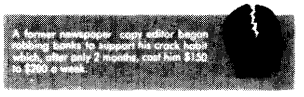
### The Scope of Use

WHERE

[illegible]

WHO

[illegible]




### Signs of Use

[illegible]

### Sources of Help

If you believe someone is in trouble with crack, you can get help and information from schools, cities, and local organizations.

Two national toll-free hotlines are:

1-800-COCAINE

This is an around-the-clock information and referral service. Referrals include public employees and private treatment programs, and self-help groups. Callers can request free publications. This hotline is sponsored by the Drug Enforcement Administration (DEA).

1-800-662-HELP

This is a national hotline for information on Drug Abuse (NIDA) of a call operator's referral to the local that directs callers to certified alcohol and drug centers in their local communities. NIDA also publishes [illegible] drug abuse. Write: National Institute of Drug Abuse, 5600 Fishers Lane, Rockville, Md. 20857.

Drug information is available from:

301-984-5700
American Council for Drug Education
5820 Hubbard Drive
Rockville, MD 20852

404-329-5709
Families in Action National Drug Information Center
Suite 300
3845 North Druid Hills Road
Decatur, Ga. 30033

1-800-258-2766
Just Say No Foundation
1777 North California Boulevard
Walnut Creek, Calif. 94596

National Clearinghouse for Alcohol & Drug Information
P.O. Box 2068
Rockville, Md. 20852

1-800-554-KIDS
National Federation of Parents for Drug-Free Youth
Suite 300
8730 Georgia Avenue
Silver Spring, Md. 20910

1-800-241-7946
Regency Recovery Institute for Drug Education (RRIDE)
Suite 1002
100 Edgewood Avenue
Atlanta, Ga. 30303

There are many sources of information and help available in your community. Check with your school district office, physicians, community health groups, clergy, or local law enforcement agencies.



[illegible] Education appreciates information contributed here provided by the U.S. Department of Justice, Drug Enforcement Administration and the National Institute of Justice, the U.S. Department of Health and Human Services, and the Office for Substance Abuse Prevention, National Drug Informa-


***Photo credit: U.S. Department of Education***

rupturing of vessels that can result in encephalopathy as well.

### Further Information

Neurobiology and toxicology are rapidly expanding scientific fields that cut across many disciplines. A brief chapter can only touch on some of the general scientific principles underlying neurotoxicology, which lies at the intersection of these two fields. The interested reader may wish to consult any of several textbooks or nontechnical books for further information.

## SUMMARY AND CONCLUSIONS

The complexity of the nervous system has made the field of neurotoxicology one of the most demanding disciplines in toxicology. In the last decade, neurotoxicologists have been able to differentiate the effects of many chemicals in terms of where they act and the symptoms they produce, but in most cases they have not yet been able to determine the mechanisms of action. Very few suspected neurotoxic chemicals have been evaluated in the laboratory and even fewer have been tested thoroughly. These chemicals act at many levels of the nervous system and exert their effects in a variety of ways, with consequences ranging from mild sensations of tingling in the extremities to severe mental retardation, loss of sensory function, and death. The chemicals may be particularly toxic to susceptible populations such as the unborn, the young, the sick, and the elderly. In order to safeguard human populations against the potentially damaging effects of these chemicals, it is necessary to study the consequences of prolonged low-level exposures as well as the effects of neurotoxic chemicals on sensitive populations.

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