

INTRODUCTION TO NEUROTOXICOLOGY

The vulnerability of the nervous system to both temporary changes and permanent damage from a wide variety of agents is increasingly evident. For thousands of years humans have searched out agents that affect the nervous system. Many people today are regular users of alcohol, caffeine, or other agents designed to affect the nervous system. Industrialization ushered in an era of rapid development of new chemicals, often accompanied by human exposure that we learned, sometimes through tragic experience, can irreparably damage the nervous system. No one can reach his or her full genetic potential with a damaged nervous system. As a consequence, neurotoxicology developed as a discipline in the 1970s to advance our understanding of the effects of chemicals on the nervous system.

What is Neurotoxicity?

Neurotoxicity or a neurotoxic effect: an adverse change in the chemistry, structure, or function of the nervous system following exposure to a chemical or physical agent

Voluntarily and involuntarily, we are exposed to a range of chemicals that affect the nervous system. We spend billions of dollars every year voluntarily purchasing chemicals such as caffeine, alcohol, and nicotine to influence our nervous system. Most stores and many industries are dependent on our desire to influence our nervous system. Many of us are familiar with the undesirable effects of too much caffeine or alcohol, which is a form of neurotoxicity. Fortunately, we quickly recover from the neurotoxic effects of caffeine or alcohol and learn to manage our consumption of these chemicals to minimize the undesirable effects and maximize the desirable effects. In this sense, many of us are experienced neurotoxicologists.

Voluntary consumption of [drugs](#) that our society has classified as illegal is also common. These drugs range from the active ingredient of the easily cultivated [marijuana](#) plant to chemicals produced in illicit laboratories. Billions of dollars are spent on the purchase of illegal drugs and in turn billions more are spent on trying to stop their manufacture and purchase. The direct and indirect costs to our society of the "war on drugs" are enormous.

A range of legal drugs is sold by the pharmaceutical industry to treat illnesses of the nervous system. Advances in our understanding of the structure and function of the nervous system has accelerated the development of chemicals for treating diseases such as Parkinson's syndrome, Alzheimer's disease, and mild depression. The treatment of mild depression with drugs like [Prozac](#) is a billion-dollar industry. However, some drugs may produce undesirable nervous system side effects that can limit their utility in disease treatment. The anticancer drugs vincristine and cisplatin damage sensory nerves in the fingers and the antibiotic gentomycin can affect hearing.

We are also involuntarily exposed to chemicals, compounds, or even physical agents that can damage the nervous system. The science of neurotoxicology has largely focused on understanding the adverse

effects of agents on the nervous system. This research has shown that the nervous system, particularly the developing nervous system, is vulnerable to permanent damage by a number of agents. For example, even low levels of lead exposure will permanently damage the nervous system of young children, reducing their ability to learn and perform well in school, and ultimately affecting their performance and quality of life as adults. Alcohol, while having a predictable effect on the pregnant mother, can be disastrous for the nervous system of the developing infant. Many workers are exposed to agents such as solvents or pesticides that can transiently affect the nervous system or even cause permanent damage. Physical agents such as noise and heat can also adversely affect the nervous system or degrade performance. Many people, including construction workers who routinely use hearing protection devices, are a testament to the awareness that excessive exposure to loud noise will permanently damage hearing.

A more formal definition of neurotoxicity or a neurotoxic effect is as an adverse change in the chemistry, structure, or function of the nervous system following exposure to a chemical or physical agent. An important part of this definition is that the effect may produce either structural change in the nervous system, such as gross cell loss, or functional changes that may be related to subtle changes in nerve cell communication. Even minor changes in the structure or function of the nervous system may have profound consequences for neurological, behavioral, and related body functions. Often the very young and elderly are more susceptible to neurotoxic effects. Lead is a good example of a compound that at high levels of exposure can cause actual nerve cell damage but at low levels, particularly in children, can cause functional losses such as decreased learning and memory.

Defining and testing for neurotoxicity is difficult because there is no one easy-to-define measure. Neurotoxicology effects can be divided into five areas (Table 17.1).

Neurological and Behavioral Effects of Exposure to Toxic Substances

Motor effects	Convulsions, weakness, tremor, twitching, lack of coordination, unsteadiness, paralysis, reflex abnormalities, activity changes
Sensory effects	Equilibrium changes, vision disorders, pain disorders, tactile disorders, auditory disorders
Cognitive effects	Memory problems, confusion, speech impairment, learning impairment
Mood and personality effects	Sleep disturbances, excitability, depression, irritability, restlessness, nervousness, tension, delirium, hallucinations

General effects	Loss of appetite, depression of neuronal activity, narcosis, stupor, fatigue, nerve damage
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Adapted from W.K. Anger (1986)

Case Studies

Caffeine

Caffeine is the most widely consumed stimulant drug in the world. It occurs naturally in coffee, tea, and the cola nut and is added to many soft drinks. Many of us consume coffee and soda drinks because of the desirable stimulatory effects produced by caffeine; many of us have consumed too much caffeine and felt the consequences. The undesirable effects of caffeine—the agitation, the inability to concentrate, the mild tremors, and the general unpleasantness—are a form of neurotoxicity. Literally your brain, and more specifically, the adenosine receptors in your brain, has too much caffeine. These effects are a reversible form of neurotoxicity as we metabolize caffeine quickly. By experience we have learned how to moderate our caffeine consumption to avoid the unpleasant side effects. A great deal of money is made from the neuroactive and physiological effects of caffeine. You can learn more about this fascinating drug in the chapter on caffeine.

Lead

The decision to use lead as a gasoline additive resulted in one of the greatest public health disasters of the 20th century. Lead from the tail pipes of cars settled as dust over wide areas and was most prevalent in high-traffic areas along city streets. Going from hand to mouth, the lead from cars and some additional lead from old lead-based paint were ingested by young children. In the 1970s and 1980s, researchers demonstrated that even low levels of lead exposure damaged the nervous system of children, confirming what the Greeks knew 2000 years ago: that "Lead makes the mind give way" (Dioscorides). Exposure of the developing nervous system to lead causes irreversible harm, degrading the learning and memory capabilities of the child and resulting in a lifetime of deficit. While lead was banned from most paint and removed from gasoline, it still remains a threat to many children living in older homes with lead paint or near areas contaminated with lead. Lead is still turning up in children's toys, jewelry, PVC plastics (as a stabilizer), and other products accessible to children. Lead is an example of a neurotoxic agent that causes permanent, irreversible damage to the developing nervous system, robbing children of their genetic potential. You can learn more about developmental effects of lead in chapter 8.

Prozac (fluoxetine hydrochloride)

[Prozac](#), produced by the pharmaceutical company Eli Lilly and Company, was first approved for the treatment of depression in Belgium in 1986. A year later, in 1987, it was approved for use in the United

States. It is now approved for use in over 90 countries and used by more than 40 million people worldwide. Needless to say it is a very profitable drug.

Prozac is commonly prescribed for treatment of mild depression, which is not uncommon as we make our way through the dramas and disappointments of life. Prozac, similar to many neuroactive chemicals, has a remarkably specific effect on one neurotransmitter. Typically, a neurotransmitter is released from one cell to communicate across a very small gap and picked up by a neuroreceptor on another cell. Once the neurotransmitter has performed its function of communicating with the other, it is either degraded or taken back up by the releasing cell to be reused. Prozac functions by blocking this reuptake, thus leaving more neurotransmitter within the cell gap to continue stimulating the receiving cell. Prozac selectively inhibits the reuptake of the neurotransmitter serotonin. The increased availability of serotonin appears to reduce the symptoms of depression. A range of drugs, including the well-known hallucinogen LSD, acts through serotonin.

MPTP and Parkinson's disease

In the early 1980s, MPTP or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was accidentally produced as a contaminant of a new compound that clandestine chemists created in their search for a synthetic heroine. Tragically, drug users exposed to MPTP developed tremors and a lack of muscle control that was very similar to symptoms of Parkinson's disease. Parkinson's disease is usually a slow-developing disease associated with the natural process of aging and the dying of cells in the brain. Further study revealed that MPTP attacked cells in a specific area of the brain that produces the neurotransmitter dopamine, the very same cells implicated in Parkinson's disease. This was the first time that a compound was clearly implicated in causing Parkinson's-like disease. Researchers immediately began searching for other compounds that might cause Parkinson's disease or interact with the aging processes to accelerate the onset of the disease. A number of studies have examined the association of exposure to some pesticides with an increase in Parkinson's disease. Researchers now use MPTP to develop animal models for finding new treatments for Parkinson's disease and to better understand the underlying progression of the disease.

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