A Small Dose of Neurotoxicology
Or
An Introduction to Toxicology of the Nervous System

Chapter 23
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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Introduction

The human brain is the most complex structure ever developed. It is only in the last few decades that we have begun to truly appreciate its flexibility, its complexity, and its vulnerability. The flexibility of the human nervous system is remarkable: when our ancient ancestors struggled for survival they were dependent on fire, hunting, and caves for shelter, while we rely on electricity, the supermarket, and central heating and cooling. For most, our ability to process complex information is far more important than our strength and reflexes. The brain's complexity is evident by the billons of cells that form more billions upon billions of connections and all this taking place in a remarkably small confined space. In turn these cells communicate using different chemicals called neurotransmitters. Neurotransmitters are frequently the target of drugs and chemicals that affect the nervous system. Prozac, a drug used to treat mild depression, affects the neurotransmitter serotonin. Lastly, the vulnerability of the nervous system to both transient affects 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 are regular users of alcohol or caffeine as well as many other agents designed to affect the nervous system. Industrialization ushered in an era of rapid development of new chemicals with every expanding use in our society often accompanied by human exposure that we then learned, through sometimes 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 in the 1970s to advance our understanding of the effects of chemicals on the nervous system.

> "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 & Herbert H. Schaumberg, in Experimental and Clinical Neurotoxicology, 1980

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 from these experiences we learn to manage our consumption of these chemicals to minimize any undesirable effects and maximize the desirable effects. In this sense, many of us are experienced neurotoxicologists.

Voluntary consumption of chemicals (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. On the hand, some drugs may produce undesirable nervous system side affects 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 affect 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 works that routinely use hearing protection devices a test 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 function 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 function 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 15.1).

Table 15.1 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

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. Fortunately, we metabolize caffeine quickly and the undesirable effects end. 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 twentieth 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 2nd BC). 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. However, lead is still turning up in children's toys, jewelry, as a stabilizer in PVC plastics, 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 a child of their genetic potential. You can learn more about developmental effects of lead from the lead chapter.

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 used 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 form one cell to communicate across a very small gap to be 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 produce 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.

Biology of the Nervous System

Overview

The nervous system can be divided into the central nervous system (CNS), which includes the brain and spinal cord, and the peripheral nervous system (PNS), which carries information to and from the CNS. The PNS is the information highway while the CNS is the coordinating center. Sensory information such as touch or pain is transmitted to the CNS by the nerves of the PNS. If we touch something hot the CNS will then command, through the PNS, to move those muscles that will withdraw us from the pain, in the case of something hot. The CNS also communicates with a number of glands and organs through the PNS. In addition to the basic functions of keeping us alive, the brain is responsible for our thinking, reasoning, and emotions.

The brain is incredibly complex. It is estimated to contain between 10 billion and 100 billion cells that form approximately 10^{15} connections; a huge number when compared to

the 42 million transistors on a state of the art microprocessor chip, 100 million times more. The information processing capabilities of the brain is enormous. The nervous system starts developing early in gestation and continues to grow and change particularly in the first few years of infancy and childhood. During development, the brain organizes into separate but interconnected areas that control different functions. For example, the area of the brain that processes visual information is located in the back of your head. During development, cells from the eyes must connect with cells of the optic nerve to move information to the visual processing center of the brain. This complex dance of one cell looking for a partner in another area of the brain is one reason the brain is so sensitive to disruption by a range of compounds.

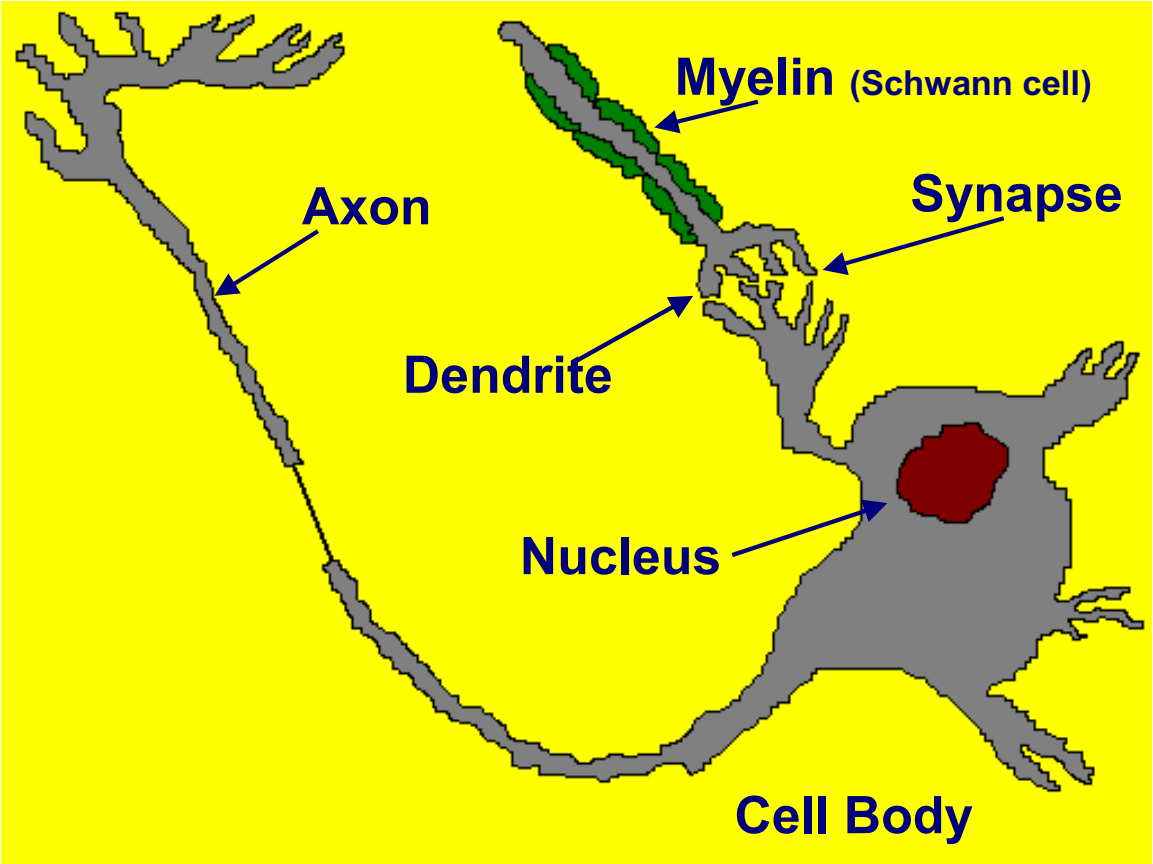
The peripheral nerves are undergoing many similar challenges. Think of the longest nerves in your body that run form the bottom of your spinal cord to your toes. These very long cells must be able to connect, grow and communicate with the right cells of the spinal cord, which in turns must communicate, with the cells of the brain.

Cells of the Nervous System

The nervous system consists of cells, called neurons (Figure 15.1), which are responsible for the majority of information transfers in the central and peripheral nerves systems and supporting cells. In the PNS, the neurons can be very long. For example, consider the information that must be sent to and from your fingers or toes to either sense touch or pain or move the muscles. The neurons have a cell body and a long connecting structure called an axon. To increase the transmission speed along the axon, another cell, a Schwann cell, wraps the axon to provide a form of insulation to facilitate the movement of electrical signals. The Schwann cells literally wrap themselves around the long axon forming multiple layers similar to tree rings. As will be discussed below these cells are susceptible to damage because of the long axon and the energy requirements of the cell.

In the CNS, glia cells aid in the communication between the densely packed neurons of the CNS. These cells also play a big part in forming the blood-brain barrier. The blood-brain barrier keeps some classes of chemicals from entering the brain, which can make it very difficult to treat diseases of the brain. However, some chemicals, such as caffeine, readily enter the brain, as do many other neuroactive compounds. Compounds essential for function are actively transported across this barrier.

Figure 15.1 Neuron in the peripheral nervous system.



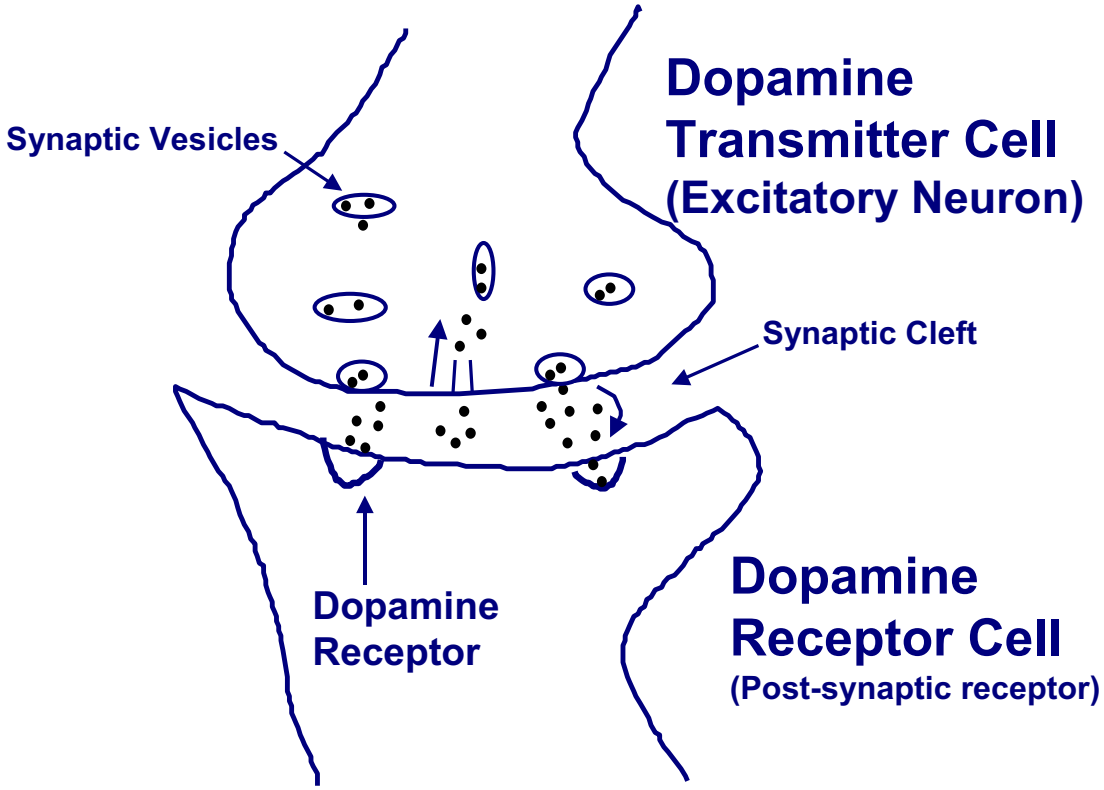
Transmission of information in the Nervous System

Nerve cells communicate by the release of chemicals (neurotransmitters) into the space between the cells (Figure 15.2). The neurotransmitter is typically stored in a small packet (synaptic vesicle) and then released in response to a signal that is transmitted down the cell axon. In the example in Figure 15.2, dopamine, an important neurotransmitter involved in movement disorders related to Parkinson's disease, is released into the gap (synaptic cleft) and reacts with specific receptors on the adjacent cell. This in turn causes a reaction in the adjacent cell. Dopamine in the gap can either be broken down or taken back up into the cell that released it and repackaged for future use.

In Parkinson's disease the dopamine-releasing cells are damaged or die, thus reducing the release of dopamine. Lose of the dopamine neurotransmitter contributes to the movement disorders associated with Parkinson's disease. Typically, the loss of dopamine-producing

cells in a very specific location in the brain does not become evident until old age, and for along time Parkinson's disease was thought of as strictly aged related. In the 1970s this concept was changed when chemists produced a designer drug meant to mimic common narcotics that had an impurity that resulted in Parkinson's like syndrome in young people never thought to be susceptible to Parkinson's disease. A specific compound, MPTP, was found to cause the death of the dopamine producing cells in the same area of the brain. While the consequence to the individuals was tragic, MPTP has proven to be a very important research tool for understanding this disease as well as developing new treatments.

Figure 15.2. Nervous system communication



What Causes Neurotoxicity?

There is no simple or correct way to examine the causes of neurotoxicity. I have divided them into three overlapping areas: neurotransmitter / receptor effects, which are often transient; damage to the peripheral nerves, which is often permanent; and damage to the developing nervous system, which is almost always permanent.

Nerve cells have unique structural and physiological features that often make them more susceptible to damage from chemical agents. Cells of the central nervous system have a high metabolic rate that makes them highly dependent on glucose and oxygen, much like computer chips need lots of electrical power. Anything that disrupts the flow of glucose or energy utilization within the cell causes a loss of function and potentially long-term damage. Nerve cells, unlike muscle cells, can only work for a very short time without oxygen. The most obvious indicator of this is that we quickly loose consciousness when our brain is deprived of well-oxygenated blood. Agents like carbon monoxide reduce the availability of oxygen to the brain resulting quickly in unconsciousness or even death. Cyanide, working by a very different mechanism, inhibits a cell's ability to utilize oxygen, which produces the same results. In the peripheral nervous system, the length of cells contributes to their increased susceptibility to damage from agents that disrupt the transfer of nutrients along the length of the cell. Acrylamide, for example, causes damage to the cell transport system, which results in paralysis that is first noticed in the legs.

In the majority of cases, the cells of the nervous system cannot divide and replace themselves, thus most damage is permanent. The developing nervous system exposed to lead will be damaged for a lifetime. However, peripheral nerves can grow, recovering some of the connections and functionality that results in some sensation and return of movement, usually most noticeable in the arms and legs.

Neurotransmitter / receptor effects

Many naturally occurring compounds and an increasing number of synthesized chemicals work by influencing the effectiveness of a specific neurotransmitter. Typically neurotransmitters are released from one neuronal cell and are picked up by specific receptors in the adjacent cell, which causes the receiving cell to react. The receptor then releases the neurotransmitter into the gap between the cells. At this time the neurotransmitter must be removed either by being broken down by a specific enzyme or it can be taken back up by the releasing cell to be reused. A compound can influence a neurotransmitter and thus the response of the receiving cell several ways: 1) blocking the receptor so that the neurotransmitter cannot reach the receptor and thus the receiving cell is unable to respond; 2) mimicking the neurotransmitter so that the receiving cell responds even though there is no naturally occurring neurotransmitter; 3) blocking the degradation of the neurotransmitter, thus leaving the neurotransmitter to react with another receptor; or 4) blocking the reuptake of the neurotransmitter into the release cell, which leaves the neurotransmitter free to again react with the receptor.

Table 15.2 provides just a few examples of different neuroactive agents and their mechanism of action. Caffeine, the most widely consumed stimulant drug in the world, works by affecting the adenosine receptor. Adenosine is a naturally occurring depressant, so caffeine works by blocking the depressive actions of adenosine, causing stimulation.

Table 15.2 Mechanism of Action of Neuroactive Agents

Compound	Neurotransmitter	Action
Caffeine	Blocks the adenosine receptor	Stimulant
Organophosphate insecticides	Increase the neurotransmitter acetylcholine by blocking its degradation	Stimulant
Nicotine	Mimics acetylcholine, thus looks like increased acetylcholine	Stimulant
Fluoxetine Prozac)	Increases serotonin by blocking its reuptake into neuronal cells	Stimulant
LSD (lysergic acid diethylamide)	Mimics serotonin, thus stimulating receptor	Hallucination
THC - Delta 9 – tetrahydrocannabinol (Cannabis)	Cannabinoid receptor	Relaxation, euphoria, and enhancement of senses, increase in appetite, sense of time
Cocaine	Blocks dopamine transporter, thus increasing dopaminergic stimulation	Increases alterness & energy, euphoria, insomnia, restlessness, fear, paranoia, hallucinations
Domoic Acid (shell fish)	Glutamate, aspartate	Loss of memory

Agents acting through a specific neurotransmitter are often transient, and exposure must be repeated to continue the effect, witness our repeated need for caffeine every morning. This is not always the case. Very potent (poisonous) nerve gases permanently block the agent responsible for degrading acetylcholine thus causing death because the nervous system cannot recover.

Damage to the peripheral nerves

The peripheral nerves of the body communicate sensation and deliver commands from the central nervous system to move muscles from our fingers to our toes – quite a distance. Peripheral nerves are wrapped by a specialized cell to form an insulation (myelin) that aids the transmission of electrical signal up along the length of the nerve cell. Agents damage the peripheral nervous system either by killing the nerve cell (neuronopathy), attacking the axon (axonopathy) or by attacking the insulation that surrounds the cells (myelinopathy) (Table 15.3 and Figure 15.3). Interfering with the neurotransmitter is a form of transmission toxicity, which was discussed in more detail above.

Table 15.3 Peripheral Nervous System Damage

Name	Type	Example
Neuronopathy	Nerve cell death	MPTP, trimethyltin
Axonopathy	Degeneration of axon	Hexane, Acrylamide
Myelinopathy	Damage to myelin (e.g. Schwann cells)	Lead, Hexachlorophene
Transmission Toxicity	Disruption of neurotransmission	Organophosphate pesticides, Cocaine, DDT

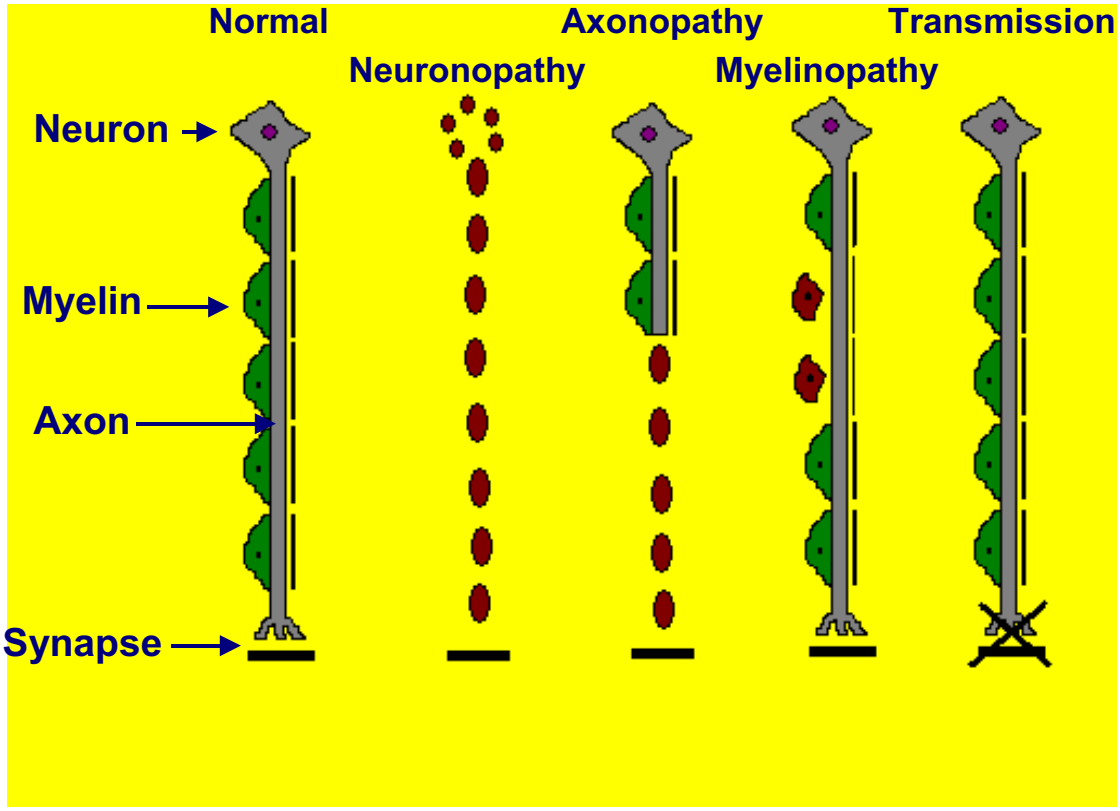


Figure 15.3 Peripheral Nervous System Damage

Damage to the developing nervous system

The developing nervous system is more vulnerable to damage than the mature nervous system for a number of reasons. The blood-brain barrier of the central nervous system is not well developed in the very young, which allows toxic agents easy access to the nervous system. The nervous system develops through our gestation and continues changing well into our teens with cells multiplying, growing in size or length, migrating

to a new location, or forming connections with other cells. During this period toxic agents may kill cells, interfere with their migration, or interfere with the cell-forming connections. Different areas of the nervous system develop at different times, so exposure to an agent such as alcohol during the fourth month of gestation will have different effects than exposure during the sixth month.

Damage to the brain can range from the severe and obvious to the very subtle and undetectable. Exposure to high levels of alcohol during gestation can cause obvious reductions the ability of a child to perform well in school and even contribute to society. More difficult to assess is the damage caused by very low levels of exposure. Low levels of exposure to alcohol or lead during development may reduce a child's IQ only slightly, by a degree that is within the normal range of variation. These more subtle changes can only be examined by comparing large groups of people, some of whom are exposed to the agent and some that are not. Group-based studies such as these were the first to show that even low levels of lead exposure during development can cause subtle decreases in IQ, thus depriving an individual of the ability to reach their full genetic potential. Any one individual would not know if their intellectual capabilities had been reduced, but on a large scale these changes have serious implications for society. Additional information is available in the lead and alcohol chapters.

Another area of concern is exposure to fat-soluble compounds such as PCBs or chlorinated pesticides. All cells contain lipids or fat; the high number of densely packed cells of the brain means that the brain is just a big ball of fat. The brain is a great storage site for fat soluble compounds can cross the blood-brain barrier. An additional concern is that these compounds can be mobilized from the fat of women breastfeeding their infants, resulting in exposure to the infant and, given the size of the infant, this exposure translates into a large dose.

Diseases of the nervous system

Can toxic agents cause what have been classically defined as diseases of the nervous system, such as Parkinson's disease, Alzheimer's type dementia, multiple sclerosis, or amyotrophic lateral sclerosis (ALS) The discovery that the chemical MPTP can cause a syndrome very similar to Parkinson's disease really focused people's attention on the possibility that chemical agents may play a role in the onset of neurological disorders once exclusively associated with aging or just bad luck. MPTP selectively damaged the same neurons, in the same area of the brain, as those responsible for Parkinson's disease. Supporting the hypothesis that chemical agents may contribute to Parkinson's disease were data showing the that incidence of this disease had increased when compared to historical patterns, which correlated with the increased use and exposure to chemicals. Additional research that the active metabolite of MPTP, that was really responsible for damaging the neurons, was very similar to the chemical structure of some pesticides. This immediately raised the question: Could pesticide exposure increase the incidence of Parkinson's disease or cause the disease to occur at an earlier age? In fact, researchers did

find some correlation with pesticide exposure in farm workers and the onset of Parkinson's disease.

Exposure to metals is associated with a number of neurological disorders, so it was reasonable to ask: Could exposure to metals contribute to age-related neurological disorders? Researchers found that brain cells of many Alzheimer's patients has elevated levels of aluminum, and kidney dialysis patients could suffer from a neurological disorder related to elevated exposure to aluminum, but much additional study has never found that aluminum exposure cause Alzheimer's disease. There is, however, some data supporting the possibility that exposure to mercury could result in accelerated age-related decline of cognitive function.

Neurological and psychiatric disorders such as depression, hyperactivity, and manic depression have driven many pharmaceutical companies and research to develop neuroactive drugs to treat these conditions. This is an active area of research that will accelerate as we gain more knowledge of the underlying mechanisms of the nervous system. Early drugs used to treat psychiatric disorders often had highly undesirable side effects that often limited their long-term use or required additional drugs to mange the complications. Newer drugs are more specific and have fewer side effects.

The following table lists a few of the examples of neurotoxicology caused by a variety of agents.

Table 15.4 History of Neurotoxicology

Year(s)	Location	Substance	Comments
400 BC to now	World wide	Lead	Hippocrates recognizes lead toxicity in the mining industry; lead used to sweeten Roman wine; modern – lead used in paint and as a gasoline additive; low level lead exposure shown to damage the nervous system of children.
Ancient	World wide	Mercury	Mine workers poisoned; 1930's hat industry (the Mad Hatters); 1950's Japan mercury in fish; 1970's mercury in seed grain; acceptance of mercury as a developmental neurotoxicant; released from coal fired electrical plants; ongoing contamination of fish
1930s	United States (Southeast)	TOCP	Compound often added to lubricating oils contaminates "Ginger-Jake," an alcoholic beverage; more than 5,000 paralyzed, 20,000 to 100,000 affected
1930s	Europe	Apiol (w/TOCP)	Abortion-inducing drug containing TOCP causes 60 cases of neuropathy
1932	United States(California)	thallium	Barley laced with thallium sulfate, used as a rodenticide, is stolen and used to make tortillas; 13 family members hospitalized with neurological symptoms; 6 deaths
1937	South Africa	TOCP	60 South Africans develop paralysis after using contaminated cooking oil
1950s	France	organotin	Contamination of Stallinon with triethyltin results in more than 100 deaths

1950s	Morocco	manganese	150 ore miners suffer chronic manganese intoxication involving severe neurobehavioral problems
1950s-70s	United States	AETT	Component of fragrances found to be neurotoxic; withdrawn from market in 1978; human health effects unknown
1956	—	endrin	49 persons become ill after eating bakery foods prepared from flour contaminated with the insecticide endrin; convulsions resulted in some instances
1956	Turkey	HCB	Hexachlorobenzene, a seed grain fungicide, leads to poisoning of 3,000 to 4,000; 10 percent mortality rate
1956-77	Japan	clioquinol	Drug used to treat travelers' diarrhea found to cause neuropathy; as many as 10,000 affected over two decades
1959	Morocco	TOCP	Cooking oil contaminated with lubricating oil affects some 10,000 individuals
1968	Japan	PCBs	Polychlorinated biphenyls leaked into rice oil, 1,665 people affected
1969	Japan	n-hexane	93 cases of neuropathy occur following exposure to n-hexane, used to make vinyl sandals
1971	United States	hexachlorophene	After years of bathing infants in 3 percent hexachlorophene, the disinfectant is found to be toxic to the nervous system and other systems
1971	Iraq	mercury	Mercury used as fungicide to treat seed grain is used in bread; more than 5,000 severe poisoning, 450 hospital deaths, effects on many infants exposed prenatally not documented
1973	United States(Ohio)	MnBK	Fabric production plant employees exposed to solvent; more than 80 workers suffer polyneuropathy, 180 have less severe effects
1974-75	United States(Hopewell, VA)	chlordecone(Kepone)	Chemical plant employees exposed to insecticide; more than 20 suffer severe neurological problems, more than 40 have less severe problems
1976	United States(Texas)	leptophos(Phosvel)	At least 9 employees suffer serious neurological problems following exposure to insecticide during manufacturing process
1977	United States(California)	dichloropropene(Telone II)	24 individuals hospitalized after exposure to pesticide Telone following traffic accident
1979-80	United States(Lancaster, TX)	BHMH(Lucel-7)	Seven employees at plastic bathtub manufacturing plant experience serious neurological problems following exposure to BHMH
1980s	United States	MPTP	Impurity in synthesis of illicit drug found to cause symptoms identical t those of Parkinson's disease
1981	Spain	toxic oil	20,000 persons poisoned by toxic substance in oil, resulting in more than 500 deaths; many suffer severe neuropathy
1984	Bhopal, India	Methyl isocyanate	December 2, 1984, an accident at the Union Carbide pesticide plant in Bhopal, India, released at least 30 tons of a highly toxic gas called methyl isocyanate,
1985	United States	aldicarb	More than 1,000 individuals in California and other Western States and British Columbia experience neuromuscular and cardiac problems following ingestion of melons contaminated with the pesticide aldicarb

1987	Canada	domoic acid	Ingestion of mussels contaminated with domoic acid causes 129 illness and 2 deaths. Symptoms include memory loss, disorientation, and seizures
1991	United States	domoic acid	Shellfish contaminated with domoic acid found in the Northwest.
2001	United States	Chlorpyrifos	Powerful insecticide phase out for home use

Adapted from: Neurotoxicity: Identifying and controlling poisons of the nervous system US Congress, Office of Technology Assessment (1990)

Who Is Vulnerable?

Without a doubt the developing fetus and child are the most vulnerable to the effects the chemicals on the nervous system. As children they have no control over these exposures that can result in a lifetime of disability. The nervous system of adults is clearly affected by a range of chemicals both those sought after and our environment.

The home, workplace, and general environment each represent unique places of possible exposure to neuroactive agents. The home contains a range of compounds that affect the nervous system: caffeine in coffee and tea, alcohol, medicines, pesticides, cleaning agents, paints, and solvents to name just a few. Compounds such a lead or pesticides can be tracked into the home on shoes or bare feet. Working family members may bring agents such as lead home on clothing. Probably the greatest concern in the workplaces is solvent exposure from cleaning agents or chemical processes. Farmers and pesticide workers can also be exposed to compounds clearly designed to affect the nervous system. The outdoor environment can contain elevated levels of a number of persistent chemicals that can adversely affect the nervous system such as lead, mercury and chlorinated pesticides.

Table 15.5 Exposure to Neurotoxic Compounds

Home	a) children during development form maternal exposure b) children – lead in the home c) cleaning agents d) solvents
Workplace	a) solvents b) pesticides
Environment	a) lead b) mercury (in fish) c) pesticides d) persistent environmental pollutants

Regulatory Standards

As our appreciation for the subtle neurological effects and long-term consequences of exposure to compounds has increased there has been a gradual increase the testing requirements for new compounds. Government agencies can now require additional testing for the neurotoxic effects of a compound. However, for many compounds we know very little about their potential to cause neurotoxicity or affect the developing nervous system. In the case of lead, there is no safety factor included in the levels of concern indicted by the Center for Disease Control but rather the standard was set based on a low level found in the general population as lead was removed from gasoline. In general, the government struggles to keep up with the ever-growing list of new chemicals and struggles to assess their potential to cause neurotoxic injury.

Recommendation and Conclusions

Many of us regularly consume compounds that affect our nervous system and are well aware of chemicals that cause neurotoxicity, so the recommendation is simple – be aware. The developing nervous system is very sensitive to neurotoxicity and exposure to the wrong chemical at the wrong time can cause a lifetime of disability. From an ethical and social perspective this vulnerability of the developing nervous represents unique challenges and responsibilities. Many of the persistent bioaccumulative toxicants are neurotoxic, which is an important augment for these compounds to be phased our or banned. Our expanding understanding of the nervous system combined with the knowledge of the subtle harm that can be done is one of the most important contributions of the toxicological sciences.

More Information and References

Slide Presentation

A Small Dose of Neurotoxicology presentation material from INND Online: www.asmalldoseoftoxicology.org

Web site contains presentation material related to the neurotoxic effects of chemicals.

European, Asian, and International Agencies

- Organization For Economic Co-Operation And Development (OECD) – Chemical Safety. Online: < https://www.oecd.org/chemicalsafety/> (accessed: 16 October 2020).
  This OECD Site contains general information on chemical safety as well as specific testing guidelines for neurotoxic effects of chemicals.

- International Neurotoxicology Association (INA). Online: <http://www.neurotoxicology.org/> (accessed: 16 October 2020).

Site provides links to neurotoxicology testing guidelines and other information on neurotoxicology.

- International Brain Research Organization (IBRO). Online: <http://www.ibro.org/> (accessed: 16 October 2020).
  "IBRO is a non-profit international organization for neuroscientists."

North American Agencies

- US Food and Drug Administration (FDA) – Neurotoxicology Division Access: Online: https://www.fda.gov/about-fda/nctr-research-offices-and-divisions/division-neurotoxicology > (accessed: 16 October 2020).
  The Division focuses on increasing FDA's understanding of the processes associated with neurotoxic outcomes—harmful effects associated with the brain and nervous system.

- US Environmental Protection Agency (EPA) Guidelines for Neurotoxicity Risk Assessment Online: < https://www.epa.gov/risk/guidelines-neurotoxicity-risk-assessment > (accessed: 16 October 2020).
  This EPA site provides information on neurotoxicity risk assessment.

- US National Institute of Health - National Institute of Neurological Disorders and Stroke (NINDS). Online: <http://www.ninds.nih.gov/> (accessed: 16 October 2020).
  NINDS is works to shape "the future of research and its relationship to brain diseases".

Non-Government Organizations

- Society for Neuroscience (SFN). Online: <www.sfn.org/> (accessed: 16 October 2020).
  "SFN is a nonprofit membership organization of basic scientists and physicians who study the brain and nervous system."

- ALS Association (ALSA) (amyotrophic lateral sclerosis). Online: <http://www.alsa.org/> (accessed: 16 October 2020).
  The mission of The ALS Association is to find a cure for and improve living with ALS.

- Developmental Neurotoxicology Society (DNTS; formerly known as the Neurobehavioral Teratology Society (NBTS). Online: http://www.dntshome.org/ (accessed: 16 October 2020).
  DNTS mission is to understand how the environment affects the health of infants and children.

Journal

NeuroToxicology is a peer-reviewed scientific journal covering research on the toxicology of the nervous system.

Wikipedia

Neurotoxicology - https://en.wikipedia.org/wiki/Neurotoxin

References

Spencer, Peter S. and Schaumburg, Herbert H. (Eds). Experimental and Clinical Neurotoxicology. Oxford University Press. 2nd edition (2000). 1152 pages.

Dobbs, Michael R. Clinical Neurotoxicology: Syndromes, Substances, Environments. Saunders (2009). 720 pages.

Harry, G. Jean, Tilson, Hugh A. Neurotoxicology, Third Edition (Target Organ Toxicology Series) Informa HealthCare; (2009). 480 pages.

Djai B. Heyer, Rhiannon M. Meredith Environmental toxicology: Sensitive periods of development and neurodevelopmental disorders. NeuroToxicology 58 (2017) 23–41.

Project TENDR: Targeting Environmental Neuro-Developmental Risks. The TENDR Consensus Statement. http://dx.doi.org/10.1289/EHP358. volume 124 | number 7 | July 2016 • Environmental Health Perspectives

Andrew D. Kraft, Michael Aschner, Deborah A. Cory-Slechta, Staci D. Bilbo, W. Michael Caudle, Susan L. Makris Unmasking silent neurotoxicity following developmental exposure to environmental toxicants Neurotoxicology and Teratology 55 (2016) 38–44

Environmental Factors In Neurodevelopmental And Neurodegenerative Disorders Edited by Michael Aschner, PhD Lucio G. Costa, PhD. Academic Press, 2015.