Chapter 6

Target Organ Effects
Neurotoxicity
General Organization of the Nervous System

• **Central nervous system (CNS)**
  – Brain
  – Spinal cord

• **Peripheral nervous system (PNS)**
  – Sensory nervous system (afferent nerves)
  – Motor nervous system (efferent nerves)
    • Somatic motor nervous system
      – To stimulate the skeletal muscles of the body
    • Autonomic nervous system (ANS)
      – Sympathetic (SNS) nervous system
      – Parasympathetic (PSNS) nervous system
• **Neuron**
  – The basic functional unit of the nervous system is the neuron. Neurons function as receptors for internal and external stimuli; they transmit the information to the central nervous system and carry impulse from there to muscles and glands.
  – The neuron is composed of the cell body (**soma**) and the axon as well as fiber-like extensions referred to as dendrites.
  – The soma contains a nucleus, a well-developed endoplasmic reticulum, and a Golgi complex.
Cells of the Nervous System (2)

• Neuron
  – Numerous mitochondria may be found throughout the cell body; they provide the energy needed to maintain and re-establish the resting membrane potential processes associated with neurons.
  – Branching cell body processes (projections or outgrowths), called dendrites, are primarily responsible for carrying impulses toward the cell body.
  – The dendrites can receive stimuli from a variety of sources such as touch, pain, or smell.
  – The axon is usually a single fiber that carries impulses away from the cell body.
    • The axons of sensory nerves carry information to the central nervous system.
    • The axons of the motor nerves carry information to the muscles and glands.
Cells of the Nervous System (3)

• Neuroglia (or glia cells)
  – The cells form the supporting elements of the nervous system.
  – The cells are non-neuronal cells that maintain homeostasis, form myelin, and provide support and protection for the brain's neurons.
  – The three types of neuroglia are:
    » astrocytes
      – They are important component of the blood-brain barrier.
    » oligodendrocytes, and
    » schwann cells.
Cells of the Nervous System (4)

- Cell processes of oligodendrocytes in the central nervous system as well as Schwann cells in the peripheral nervous system surround the nerve cell axons. This facilitates the transmission of impulses along the axon.
  - If the axon simply lies within an indentation of an oligodendrocyte or Schwann cell, it is referred to as an unmyelinated nerve.
  - Oligodendrocyte processes or Schwann cells may wrap around the axon forming several concentric layers of membrane called a myelin sheath. These types of axons are referred to as myelinated nerves.
  - The myelin sheath is an efficient insulator and does not allow easy movement of ions, particularly sodium and potassium, into and out of the axon --- an important factor in maintaining the membrane potential and in the generation of action potential.
Cells of the Nervous System (5)

- Neuroglial cells are important in regulating ion balance, in the absorption of substances from the blood-stream, and in maintaining normal nerve cell functioning.
General Physiology of the nervous System (1)

• Detection of stimuli and the initiation of responses are the result of electro-chemical events associated with the nervous system.
• Upon receiving a stimulus, such as pain or the sensation of heat, the membrane of the neuron undergoes a change in permeability resulting in the movement of sodium and potassium ions across the cell membrane. This generates an electrical charge called the action potential.
• The action potential travels along the nerve cell and eventually arrives at the end of the axon, where it causes the release of a chemical substance referred to as a neurotransmitter.
• The neurotransmitter is responsible for initiating a response in another nerve cell, muscle, or gland.
• **Action potential**
  – The action potential associated with an axon or with a group of axon (referred to as nerves) is responsible for carrying information from the source of the stimulus to the central nervous system by the afferent nerves.
  – The action potential is generated when the ion distribution across the cell membrane is changed. During the “resting phase” there is a positive charge on the outside and a negative charge on the inside of the nerve cell membrane.
  – An uneven distribution of ions, particularly Na$^+$ and K$^+$, is responsible for establishing the resting membrane potential.
  – There is a higher concentration of sodium ions on the outside of the cell than inside.
General Physiology of the nervous System (3)

- When a neuron is stimulated the cell membrane of the dendrite becomes more permeable to sodium ions.
- The inside of the cell becomes positively charged, while the outside of the cell temporarily becomes negatively charged.
- Potassium ions then diffuse out of the cell in response to the influx of sodium ions.
- These changes cause the adjacent portion of the cell membrane to depolarize, and a wave of depolarization (action potential) passes down the cell to the end of the axon resulting in the release of the chemical neurotransmitter, which then stimulates the affected tissue.
Chemical Neurotransmitters

- There are several chemical neurotransmitters associated with the nervous system. The best known are acetylcholine and norepinephrine. Neurotransmitters are released from the end of the axon and interact with other neurons, glands, or muscles.

- The junction where the neuron interacts with another cell is referred to as a synapse. The end of the axon is referred to as the presynaptic terminal. The cell membrane of the stimulated tissue is referred to as the postsynaptic membrane. The space between these two structures is the synaptic cleft.

- In order for the affected tissue not to be constantly stimulated, the neurotransmitter is broken down rapidly by enzymes, or is reabsorbed by the presynaptic terminal.
Neurotoxic Effects (1)

• The effects of toxic substances on neurons may be placed into two categories:
  – those that affect the neuron structure, and
  – those that affect the neurotransmission between the presynaptic terminal and the postsynaptic membrane.

• The kind of damage that occurs can be classified as neuropathy, axonopathy, or myelinopathy.
  – Neuropathy (neuron destruction) is caused by the interaction of toxic substances primarily with the nerve cell body (soma).
    • methyl mercury
    • manganese
    – High concentrations of manganese can result in damage to the central nervous system, particularly the brain.
    – Symptoms are neuropsychiatric in nature and are characterized by irritability, difficulty in walking, and speech abnormalities. Continuous, prolonged exposure can cause symptoms similar to Parkinson’s syndrome, which is characterized by tremors and spastic contractions of skeletal muscle.
– Acute methanol exposure can result in nerve damage leading to blindness or death. Visual problems will begin to occur including eye pain, blurred vision, and constriction of the visual fields.

• Axonopathies are characterized by damage to the axon. Acrylamide, carbon disulfide, and hexacarbons such as n-hexane, all cause axonopathies. Exposure to these substances is characterized by loss of peripheral sensations and progressive impairment of skeletal muscle functioning.
  – Acute exposure to organophosphate pesticides affects normal synaptic activities and can lead to delayed effects characteristic of axonopathy. Degeneration of the axon does not begin until seven to ten days after acute exposure.
Neurotoxic Effects (3)

- **Myelinopathy**
  - Loss of the myelin sheath results in impairment or loss of transmission of the nerve impulse.
  - Hexachlorophene is an antimicrobial substance that was used in fungicides and pesticides and is still found today in germicidal soaps and detergents. Hexachlorophene easily penetrates the skin and once in the body it is absorbed into the myelin sheath surrounding the nerves.
  - Acute and chronic exposure of young children to lead result in different symptoms. Acute exposure can result in excess accumulation of fluids in the brain. If this condition persists for a prolonged period of time it can result in mental retardation or, if severe enough, death. Chronic, low-level exposure to lead seems to be correlated with learning disabilities. Lead appears to produce its effects by more than one mechanism---demyelination and axonopathy.
Neurotoxic Effects (4)

- Neurotransmission toxicity
  - Neurons release only one type of neurotransmitter substance.
  - Various types of toxic substances interrupt the normal sequence of events associated with neurotransmission between the presynaptic terminal and the postsynaptic membrane.
  - Based upon their mechanism of action, they may be categorized as:
    - blocking agents
    - depolarizing agents
    - stimulants
    - depressants
    - anticholinesterase agents
Neurotoxic Effects (5)

• **Blocking agents**
  – The toxin binds to the presynaptic terminal and prevents the release of acetylcholine.
  – A toxin produced by the bacterium *Clostridium botulinum* is responsible for the illness referred to as botulism.

• **Depolarizing agents**
  – Depolarizing agents eliminate the resting membrane potential by altering the permeability of the cell membrane towards sodium and potassium ions.
  – DDT partially depolarizes the presynaptic neuron membrane. It increases the cell membrane permeability to sodium and decrease it to potassium.
Neurotoxic Effects (6)

• Stimulants
  – Toxic substances that are classified as stimulants increase the excitability of neurons.
  – Nicotine exerts its effects by binding to and stimulating a subset of receptors that normally bind acetylcholine, called nicotinic receptors.
  – Caffeine is a stimulant of the central nervous system. It appears to produce this effect by affecting the active transport system that maintains the sodium/potassium concentration gradient across the cell membrane.
  – Cocaine easily crosses the blood-brain barrier where it is able to produce its euphoric and addictive effects. It inhibits the reabsorption of a group of neurotransmitters, called catecholamines, into the presynaptic neuron.
• Stimulants
  – Cocaine easily cross the blood-brain barrier where it is able to produce its euphoric and addictive effects. It inhibits the reabsorption of a group of neurotransmitters, called catecholamines, into the presynaptic neuron. Epinephrine, norepinephrine, and dopamine are catecholamines. Normally, these neurotransmitters are reabsorbed and broken down in the presynaptic neuron.
  – Inhibition of the reabsorption allows the neurotransmitters to remain in the synaptic cleft region. This results in continuous stimulation of the postsynaptic membrane of the affected tissue.
Neurotoxic Effects (8)

• Depressants
  – Some volatile organic toxicants decrease the excitability of neurons.
  – The decreased sensitivity may be related to the ability of these substances to prevent normal ion exchange ($\text{Na}^+$, $\text{K}^+$, and $\text{Ca}^{2+}$) across the cell membrane, which affects the resting membrane and action potentials.
  – Aromatic organic solvents that consist of one or more benzene rings have a depressant effect on the central nervous system.
  – Alcohol are powerful central nervous system depressants. Ethanol primarily affects the central nervous system resulting in bradycardia (slow heart rate) and dilation of the blood vessels, which in large doses may lead to cardiac arrest.
Neurotoxic Effects (9)

- **Anticholinesterase agents**
  - Toxicants that are classified as anticholinesterase agents affect only those nerves that released and those that are stimulated by the neurotransmitter acetylcholine.
    - For example, organophosphate pesticides (parathion, malathion, diazinon, etc.)
    - Carbamate insecticides (carbaryl or Sevin, aldicard, etc.) have similar effects as organophosphate pesticides. They bind to the acetylcholinesterase enzyme and inhibit the breakdown of acetylcholine.
Hematoxicity (1)

• Stem cells located in the bone marrow. The stem cells give rise to:
  – the red blood cells (RBCs) or erythrocytes,
  – the white blood cells (WBCs) or leukocytes, and
  – the platelets or thrombocytes.

• The white blood cells can be divided into two types: granulocytes and agranulocytes. There are three kinds of granulocytes: neutrophils, eosinophils, and basophils.
Hematoxicity (2)

- HSC=Hematopoietic stem cell, Progenitor=Progenitor cell,
- L-blast=Lymphoblast, Lymphocyte, Mo-blast=Monoblast, Monocyte, Myeloblast, Pro-M=Promyelocyte, Myelocyte, Meta-M=Metamyelocyte, Neutrophil, Eosinophil, Basophil, Pro-E=Proerythroblast, Baso-E=Basophilic erythroblast, poly-E=Polychromatic erythroblast, Ortho-E=Orthochromatic erythroblast, Erythrocyte, Promegakaryocyte, Megakaryocyte, Platelet
Hematoxicity (3)

- Neutrophils are primarily involved in the phagocytosis of bacteria and foreign matter circulating throughout the body.
- Eosinophils are involved in the inflammatory response.
- Basophils comprise 0.5~1 percent of the leukocytes. The nucleus has two indistinct lobes, and the granules stain a dark purple.
- These cells release histamine, which promotes inflammation, and heparin, which prevents blood clot formation.
Hematoxicity (4)

• The agranulocytes include lymphocytes and monocytes.
  – Lymphocytes are characterized by a large nucleus surrounded by a thin ring of cytoplasm. The monocytes are the largest of all leukocytes and can be distinguished by a kidney or horsehose-shaped nucleus.
  – Monocytes migrate out of the blood, enlarge, and become macrophages.
  – Red blood cells are by far the most common and numerous cellular component of the blood. There are 4.2~5.8 million/mm$^3$ of blood.
    • Only about 20% of the carbon dioxide is carried by the hemoglobin molecule. A majority of the carbon dioxide is converted to a bicarbonate ion by an enzyme in the red blood cells and transported in this form; the other 8% is dissolved in the plasma.
Hematoxicity (5)

- Platelets or thrombocytes are small cell fragments. They consist of a small amount of cytoplasm surrounded by a cell membrane.
  - There are 150,000 to 400,000 platelets per mm$^3$ of blood.
Blood Cell Hematopoiesis

- **Hematopoiesis** is the process of blood cell formation.
  - The blood cells are derived from a single, multipotential cell referred to as stem cell or hemocytoblast.
  - Hematopoiesis occurs in red blood marrow and is the result of stem cell differentiation.
Hematoxic Effects (1)

• Changes in the number and type of circulating blood cells can be classified as anemia, granulocytopenia, thrombocytopenia, lymphocytopenia, or pancytopenia.

• Anemia
  – Anemia is the condition resulting from a decrease in the number of red blood cells, a decrease in the size of the red blood cell referred to as microcytic anemia, a decrease in red blood cell hemoglobin in content, or a combination of any these factors.
    • Insecticides, benzene, lead, methylene chloride, nitrobenzene and naphthalene are all capable of red blood cell destruction.
    • Lead decreases hemoglobin synthesis by inhibiting enzymes involved in the transport of amino acids used to synthesize the protein portion (globin) of the molecule.
Hematoxic Effects (2)

• Aplastic anemia
  – Toxic chemical substances such as carbon tetrachloride, chlordane (pesticide), benzene, and physical agents like ionizing radiation, can affect the bone marrow directly, suppressing the production of red blood cells, which leads to a condition known as aplastic anemia.

• Nephrotoxicity-induced anemia
  – The kidney is the source of erythropoietin, which it releases in response to low oxygen levels in the blood and which stimulates bone marrow to produce more red blood cells.
    • Mercury and cadmium affect the normal functioning of the kidneys may induce anemia by decreasing the secretion of erythropoietin.
Chemically Induced Hypoxia (1)

• Hypoxia is any condition in which inadequate amounts of oxygen are delivered to the tissues.

• Carbon monoxide-induced hypoxia
  – The affinity of hemoglobin for carbon monoxide is approximately 225 times greater than that for oxygen. Therefore, carbon monoxide displaces oxygen in the red blood cells.

• Methemoglobinemia
  – The hemoglobin molecule contains an iron atom in the ferrous state (Fe$^{2+}$). Exposure to certain toxic chemicals --- such as sodium nitrite, hydroxylamine hydrochloride, or nitrobenzene --- converts the ferrous atom to the ferric state (Fe$^{3+}$) resulting in the conversion of hemoglobin to methemoglobin (MetHb). MetHb does not bind to oxygen and therefore reduces the supply of oxygen to body tissues.
Chemically Induced Hypoxia (2)

• Cytotoxic (histotoxic) hypoxia
  – Certain toxic chemicals produce symptoms that mimic chemically induced hypoxia without changing the oxygen-carrying capacity of the blood. Exposure to hydrogen cyanide or hydrogen sulfide interferes with the ability of cells to use oxygen.
  – Thus, the body reacts by increasing heart rate and respiratory rate as a result of a perceived decrease in blood-borne oxygen.

• Granulocytopenia, lymphocytopenia, and thrombocytopenia
  – Granulocytopenia, lymphocytopenia, and thrombocytopenia are the result of a decrease in granulocytes, lymphocytes, and thrombocytes (blood platelets), respectively. These conditions occur primarily as a result of suppression of stem cell proliferation and differentiation. Benzene, carbon tetrachloride and trinitrotoluene are capable of suppressing each of these cell types.
Chemically Induced Hypoxia (3)

• Leukemia
  – Leukemia is characterized by a higher than normal number of leukocytes in the bloodstream. Benzene is probably the best known toxicant responsible for causing leukemia.
Immunotoxicity

• Structure and function of the immune system
  – The major components of the immune system are the cells of the lymphatic system, the cellular components of the blood, and the blood-borne proteins called antibodies.
Immunotoxicity --- Lymphatic System

• Lymph is fluid derived from the plasma of the blood. Liquid from the blood is filtered through the capillary walls and into the space located between cells (interstitial space).

• Before the lymph is returned to the blood, it passes through structures referred to as lymph nodes.
Storage of Toxic Substances (14)

• Unbound metals like Cd and Hg can be reabsorbed by active transport mechanisms in the cells of the proximal convoluted tubule. Once in the cell they bind to metallothionein resulting in concentration of these toxicants in the kidneys, possibly causing adverse effects.

• The kidneys store 10 times the amount of Cd found in the liver, and it can be stored for 10 years or more.

• Bioaccumulation in the kidneys may ultimately cause kidney damage and, if severe enough, result in complete renal failure.
Storage of Toxic Substances (15)

• Storage in fat
  – Storage of toxicants in the fat initially results in a lower concentration of the toxicant reaching the target tissue. Like storage in the plasma protein, liver and kidneys the toxic substance in the fat is in equilibrium with the toxicant in the blood.
  – Larger amounts of the toxicant are released when fat reserves are mobilized in response to increased metabolism of fats, such as during periods of fasting or starvation. Therefore, signs of intoxication may occur under starvation condition even though they may not have appeared during the initial exposure.
Storage of Toxic Substances (16)

• **Storage in bone**
  
  – Bone is the major storage site for calcium in the body. It is composed of bone cells called **osteocytes** and an extracellular matrix arranged in sheets called lamellae.
  
  – The extracellular matrix is composed of a mineral complex called hydroxyapatite, which is composed primarily of calcium and phosphate ions.
  
  – When blood levels of calcium are low, the hydroxyapatite is broken down, and calcium is released from the bone into bloodstream. When the calcium levels increase in the blood, calcium is absorbed into the hydroxyapatite of the bone.
  
  – It is during the exchange between blood and bone that calcium can be replaced by toxic substances such as lead and strontium.
Storage of Toxic Substances (17)

- These substances have a similar size and electrical charge as calcium. 90% of the total body burden of lead is in the bone. Significant amounts can remain in the bone for 10~20 years.

- Storage of toxic substances in the bone may or may not have a detrimental effect. Lead is not toxic to bone. However, it may be released from the bone resulting in nerve damage. Mobilization of the lead can occur in older individuals suffering from osteoporosis.
Mobilized lead in the bone of expectant mothers may be passed on the fetus. The nervous system of the fetus is very susceptible to the toxic effects of substances such as lead and may result in birth defects associated with the nervous system.

The hydroxide ion (OH\(^-\)) is also a component of the metabolic process associated with bone metabolism. Chronic exposure to elevated levels of fluoride may result in the fluoride ion (F\(^-\)) replacing the hydroxide ion during normal bone metabolism. Increased deposition of fluoride in the bone can result in fluorosis, which is characterized by weakening of the bone.
Specialized Barrier: Blood-Brain Barrier (1)

• The blood-brain barrier is created by the close association of brain capillaries with specialized cells formed in the nervous system. This barrier effectively decreases the type and amount of toxic substances that are transferred from the blood to the brain tissue.

• Reduced absorption of toxicants is attributed to several unique characteristics associated with the blood brain barrier:
  – the closely packed endothelial cells of the capillaries;
  – the astrocytes; and
  – The low protein content of the interstitial fluid.
Specialized Barrier: Blood-Brain Barrier (2)

• Normally, capillary endothelial cells are loosely joined to each other with pores, about 4 nm in diameter, located between the cells. The capillary endothelial cells of the blood-brain barrier are more closely arranged to each other, therefore, few or no pores exist.

• Lipid-soluble substances like ethanol easily diffuse through the phospholipid cell membrane and into the fluid surrounding the brain. Water soluble substances such as glucose --- which is necessary for nerve cell functioning --- must be transported across the blood-brain barrier by carrier-mediated mechanisms.
Specialized Barrier: Blood-Brain Barrier (3)

- The capillaries are surrounded by cellular processes from astrocytes. Astrocytes are specialized cells found in the nervous system.
- The cell membrane of the astrocyte has a high lipid content that helps to form an effective barrier, slowing the rate of movement of water-soluble molecules.
- The interstitial fluid is the liquid between the external wall of the capillary and the cell membrane of the surrounding tissue; it has a low protein content which reduced amounts of the protein-toxic substance complex reaches the brain tissue.
- The hydrophobic cell membrane of the astrocyte processes slows or inhibits the passage of toxicants.
Redistribution of Toxic Substances

- Toxic substances have a tendency to concentrate initially in well perfused tissues such as the liver and kidneys. However, other tissue types may have a greater affinity for the toxicant and over time --- because of the dynamic equilibrium discussed previously --- the toxicant will eventually be transported and stored in these tissues.
Metabolism (biotransformation)

• The difference in toxicity between genders seems to be primarily influenced by the sex hormones (estrogen and testosterone), which can affect metabolism.

• Some organophosphate pesticides are more toxic to females than males.
  – Parathion is metabolized more rapidly in females resulting in a higher concentration of the more toxic intermediate, paraoxon.
  – Male rats are 10 times more susceptible to liver damage than female rats as a result of chronic oral exposure to DDT.
State of Health

• The liver and the kidney are important organs for detoxifying and removing toxic substances. Therefore, conditions that lead to liver or kidney disease enhance the toxic effects of substances normally detoxified by these organs.
Hematopoiesis in humans

**Notes**
- Approximate scale information: 10 μm
- The morphological characteristics of the hematopoietic cells are shown as seen in a Wright's stain, May-Grünwald-Giemsa stain or May-Grünwald-Giemsa stain. Alternative names of certain cells are indicated between parentheses.
- Certain cells may have more than one characteristic appearance. In these cases, more than one representation of the same cell has been included.
- Together, the monocyte and the lymphocytes comprise the agranulocytes, as opposed to the granulocytes (basophil, neutrophil and eosinophil) that are produced during granulopoiesis.
- B., N. and E. stand for Basophilic, Neutrophilic and Eosinophilic, respectively – as in Basophilic promyelocyte.

1. The polychromatic erythrocyte (reticulocyte) at the right shows its characteristic appearance when stained with methylene blue or Azure B.
2. The erythrocyte at the right is a more accurate representation of its appearance in reality when viewed through a microscope.
3. Other cells that arise from the monocyte: ostoclast, microglia (central nervous system), Langerhans cell (epidermis), Kupffer cell (liver).
4. For clarity, the T and B lymphocyte are split to better indicate that the plasma cell arises from the B-cell. Note that there is no difference in the appearance of B- and T-cells unless specific staining is applied.
Lymphatic System

- Tonsil
- Thymus Gland
- Spleen
- Lymph Nodes
- Lymphatic Vessels
Lymph Capillaries in the Tissue Spaces

- Lymph capillary
- Arteriole
- Tissue fluid
- Tissue spaces
- Tissue cells
- Venule
- Lymphatic vessel