Chapter 5

Absorption, Distribution, Metabolism, and Elimination of Toxics
Introduction

• The amount toxicant that actually reaches the target tissue is dependent upon the amount absorbed, the distribution of the substance throughout the body, the metabolism (change in the chemical and physical characteristics) of the substance, and the rate of excretion.

• The amount of a substance that actually reaches the target tissue is the net result of the interaction between absorption, distribution, metabolism, and excretion.
Absorption of Toxic Substances

- The cell membrane is selective permeable; therefore, only certain substances are able to pass through it.

- The selective permeability is determined by molecular size, lipid solubility, and electrical charge associated with the toxic molecule, as well as by cell membrane active and passive transport mechanisms.

- The amount and rate of toxic substance transported across these barriers is determined by the characteristics associated with cell membrane transport and the physico-chemical attributes of the toxic substance.
Mechanisms of Absorption (1)

- Passive diffusion
  - Most toxic substances move across the cell membrane by diffusion.
  - Diffusion is dependent on three basic factors:
    - the concentration gradient across the cell membrane,
    - lipid solubility, and
    - The electrical charge associated with the molecule.

  - The rate of diffusion is primarily based on the differences in the concentration of the substance across the cell membrane, the surface area and thickness of the cell membrane.
  - Lipid solubility is also an important factor in determining the diffusion rate of a toxic substance since 75% of the cell membrane is composed of lipids.
Mechanisms of Absorption (2)

- The electrical charge associated with a toxic substance molecule or atom will also affect the rate of diffusion.
  
  » In general, nonionized toxic substances diffuse more readily across the cell membrane than ionized substances.
  
  » Organic substances such as nitrous oxide, ethylene, and divinyl ether diffuse across the cell membrane of the alveoli easily because they do not have an electrical charge and are lipid-soluble.
Mechanisms of Absorption (3)

• Carrier-mediated transport
  – Facilitated diffusion (transport) and active transport are important when:
    • moving molecules across the cell membrane against a concentration gradient;
    • the size of the toxic molecule is too large to diffuse through the pores of the cell membrane; and
    • there is low lipid solubility and the substance has an electrical charge associated with it.
  – When toxic substances are present in the small intestine, in some cases they will compete with the nutrients for the binding sites associated with the active transport mechanism.
    • For instance, calcium is actively transported from the small intestine across the cell membrane by a calcium-binding protein (CaBP).
    • Toxic substances such as cadmium, lead or strontium will also bind to the CaBP because their physio-chemical characteristics are similar to calcium.
Mechanisms of Absorption (4)

- High protein diets appear to reduce the toxicity of lead and cadmium, because amino acids derived from proteins compete for the same protein-carrier molecules.

• Facilitated diffusion
  - It is characterized by a cell membrane protein attaching to a substance outside the cell and transporting it across the cell membrane. This is similar to the active transport mechanism.
  - No energy is expended and transport of the substance is from an area of high concentration to an area of low concentration.
  - This mechanism is used to transport substances that are too large to diffuse through the cell membrane pores or that have an electrical charge associated with them.
Mechanisms of Absorption (5)

• Phagocytosis and pinocytosis
  – Phagocytosis plays an important role in the disposition of particulates that enter the respiratory tract.
  – Particulates such as asbestos, silica dust, or uranium dioxide are engulfed by white blood cells found throughout the respiratory tract, particularly the alveoli.
  – These particulate-containing cells may then remain in the respiratory system or be transported out of the systems by the ciliary-clearance mechanism.
  – Pinocytosis occurs frequently in the lining of the lumen in the small intestine. Water soluble substances and particulates appear to be transported via this mechanism.
Dose-Response Curves (2)

• The threshold is the dose below which no effect is detected or above which an effect is first observed.

• The threshold information is useful information in extrapolating animal data to humans and calculating what may be considered a safe human dose for a given toxic substance.

• The threshold dose (ThD$_{0.0}$) is measured as mg/kg/day. It is assumed that humans are as sensitive as the test animal used. To determine the equivalent dose in man the ThD$_{0.0}$ is multiplied by the average weight of a man, which is considered to be 70 kg.
Skin Absorption (1)

- All toxicants that pass through the skin do so as a result of passive diffusion.
- The rate at which a toxic substance is absorbed is determined by
  - its ability to penetrate the keratinized outer layer of the epidermis;
  - the physico-chemical properties of the toxic substance.
- Absorption is enhanced as a result of damage to the skin’s outer layer.
- Application of certain chemicals such as methyl and ethyl alcohol, hexane, and acetone are lipid-soluble and can be used to alter skin permeability by degrading the lipid barrier of the cell membrane.
Skin Absorption (2)

• Absorption of toxic substances is enhanced in areas of the skin with a well developed blood supply.

• Once the substance diffuses through the epidermis it is absorbed into the bloodstream, which will carry it to other parts of the body.
Lung Absorption (1)

- Gases and vapors of volatile compounds diffuse across the alveolar cell membrane and are absorbed into the bloodstream.

- Although lipid solubility is important in determining the rate of absorption, an even more important factor is the solubility of the toxic substance in the blood and its interaction with components of the blood.
Lung Absorption (2)

- Particulates 5 μm or larger in diameter are usually trapped in the nose and upper portions of the respiratory tract. These particles are removed from the respiratory tract by nose wiping, blowing, or by sneezing.

- Particulates 2~5 μm in diameter are trapped in the trachea and bronchial region of the respiratory tract. These particles are primarily removed by the mucociliary-escalator.

- Particles 1 μm in diameter and smaller reach the alveoli. These particulates may be dissolved and absorbed into the bloodstream.

- Some particulates (asbestos, fiberglass) that are phagocytized remain in the lungs where they may have adverse effects and result in the development of respiratory disease.
Gastrointestinal Absorption

- Most of the absorption in the digestive tract occurs in the small intestine.

- The primary mechanism of absorption is by diffusion but, as we already know, facilitated and active transport also occurs.

- Increase absorption will occur if food containing the toxic substance remains in the digestive tract for a longer period of time.
Distribution of Toxic Substances (1)

• Absorption into and out of the bloodstream occurs in only one part of the circulatory system: the capillaries.

• [Anatomy of the circulatory system]
**Anatomy of the heart**

- The right atrium receives low-oxygenated blood from the systemic (body) circulation and the left atrium receives oxygen-rich blood from the lungs.

- The ventricles are thick, muscular chambers. The right ventricle pumps blood through the pulmonary artery to the extensive vascular network (pulmonary circulation) located in the lungs.

- The pulmonary capillaries are in close association with the alveoli of the lungs; this facilitates the diffusion of substances --- such as oxygen, carbon dioxide, or airborne toxic substances --- between the circulatory system and inhaled air.

- Oxygenated blood returns to the left ventricle via the pulmonary veins and left atria.
Distribution of Toxic Substances (3)

• Anatomy of the vascular system
  – Arterioles are small-diameter arteries; the blood flows from arterioles to capillaries.
  – Venules are small veins that collect blood from capillaries; several venules unite to form larger veins.
  – There are 10 billion capillaries in the body. They are composed of a single layer of flat endothelial cells, having a diameter of 4-8 μm, and are the principal site of exchange of substances between the blood and the surrounding tissues.
  – Diffusion is the primary mechanism responsible for the movement of gases, lipid-soluble substances, and water-soluble molecules.
Distribution of Toxic Substances (4)

• The limiting factor --- in terms of transporting toxic substances from the capillaries --- appears to be the size of the molecule.

• Pinocytosis seems to be the major mechanism for transporting these types of substances. Pinocytosis is a relatively slow process; therefore, large toxic molecules will remain in the blood for a longer period of time.

• The competition for protein-carrier molecules may affect the rate of absorption and subsequent toxicity of a substance.
There are several mechanisms that oppose distribution to the target tissue:
- binding to plasma protein;
- distribution to storage sites; and
- specialized barriers.

Binding to plasma proteins
- When toxic substances enter the bloodstream they may bind with plasma proteins such as albumin, transferrin, globulin, and lipoproteins.
- Most toxic substances will bind with the plasma protein albumin.
- There is always some portion of the toxic substance that is not bound and is in equilibrium with the bound portion.
• As the undound toxicant passes through the endothelial cells of the capillary into the extravascular space (a space between the wall of the capillary and the tissue cell membrane, filled with fluid), the bound toxicant disassociates (separates) from the protein to maintain an equilibrium between the bound and unbound toxicant in the blood.

• The amount of free toxicant in the extravascular space is in equilibrium with the amount of free toxicant in the blood.

• A dynamic equilibrium exists between the bound and unbound forms of a toxicant. The equilibrium will be determined by factors that affect absorption, subsequently affecting toxicity.
Storage of Toxic Substances (1)

• The toxicants may be stored in the target tissue, possibly resulting in an adverse response, or it may be stored in other tissue types, which may not be readily affected.

• The toxicants are fat-soluble and are easily absorbed into fatty deposits throughout the body where they may be stored for long periods of time.
  – Lead is readily absorbed and stored in bone. Lead also affects nerve tissue.
  – In general, storage of these substances in these tissue types will have no effect on their primary target tissue, the nerve tissue.
Storage of Toxic Substances (2)

• Liver and kidneys have a high affinity for toxic substances and store more toxicants than any other tissue in the body. The reason for the high affinity is not clearly understood but may be attributable to anatomical and physiological characteristics associated with both organs.

• The ability to concentrate toxic substances in these organs is advantageous for the detoxification and the excretion of toxic substances; however, it may also increase the occurrence of adverse effects in the liver and kidneys.
Storage of Toxic Substances (3)

- **Structure of the liver**
  - The liver is the single largest organ of the body and can weigh as much as 1.4 kg. It is comprised of two lobes, each of which is divided into numerous functional units called lobules. A lobule consist of cords of liver cells arranged around a central vein.
  - Most venous blood passes through the liver before it reaches the heart. The liver receives blood from the lower extremities, kidneys, spleen, and gastrointestinal tract. The hepatic portal vein carries nutrient rich, but oxygen poor blood from the digestive tract to the liver.
Storage of Toxic Substances (4)

- The blood from the branches of the hepatic portal vein passes into spaces called hepatic sinusoids located between the lobular cords. In the sinusoids, venous blood is mixed with oxygen-rich and nutrient-poor blood from the hepatic artery, the second major source of blood to the liver.

- The blood from the sinusoids drains toward the center of the lobule and into the central vein and then exists the liver through the hepatic veins.
Absorption of toxic substances in the liver is affected by the same factors that regulate absorption in other tissue types.

Lipophilic substances, such as organochlorine pesticides and organic solvents (trichloroethane, methyl chloroform), are readily absorbed. If they are not biotransformed into water-soluble substances they will be retained in the liver for long periods of time.

Active transport mechanisms facilitate concentration of toxicants in the liver, subsequently causing liver damage. The hepatocytes absorb copper ($Cu^{2+}$) and iron ($Fe^{2+}$) from the blood by protein-carrier molecules in the cell membrane.
Storage of Toxic Substances (6)

• The liver is a major storage site for water-insoluble toxic substances such as heavy metals.

• There are two other features associated with the liver, which facilitate the absorption and concentration of toxicants.
  – As it passes through the liver, the blood enters the sinusoids located between strands of hepatocytes. The layer of endothelial cells lining the sinusoids is discontinuous with small and large fenestrae (pores). The fenestrae allow larger, blood borne molecules to pass through the endothelial lining and to be absorbed by the hepatocytes.
  – The liver cells also have a high concentration of the intracellular protein metallothionein. Methallothionein has a high affinity (binding up to 99%) for many different kinds of toxic metals such as Cd, Hg and Pb.
When bound to metallothionein the protein metal complex does not readily pass through the cell membrane. Therefore, the affinity of metals for the cell membrane transport mechanisms, the presence of fenestrae, and the high affinity of metals for intracellular metallothionein facilitate the storage of some toxicants in the liver at higher concentrations than in the surrounding tissue.
• Structure and function of the kidneys
  – The **kidneys** are two bean-shapes organs located on the posterior wall of the abdominal cavity. Each kidney is divided into two parts, the outer portion referred to as the cortex and the inner portion referred to as the medulla.
  – Within the medulla are cone-shaped structures called renal pyramids. Urine passes from the tips of the pyramids to a large funnel-like structure called the **renal pelvis**. The renal pelvis narrows to form the ureter, which connects the kidneys with the urinary bladder.
Storage of Toxic Substances (9)

- The functional unit of the kidney is the nephron, parts of which are found in the renal cortex and the medulla. There are approximately 1.3 million nephrons in each kidney.

- Each nephron is composed of the following structures:
  - renal corpuscle
  - a proximal convoluted tubule,
  - a Loop of Henle
  - a distal convoluted tubule

- The distal convoluted tubule empties into a collecting duct, which transports urine toward the renal pelvis area where it enters the ureter.
Storage of Toxic Substances (10)

• The renal corpuscle is composed of Bowman’s capsule and a ball-like arrangement of capillaries referred to as the glomerulus.

• Substances carried in the blood are transported to the renal corpuscle of the nephron.

• The kidneys receive approximately 25% of the total cardiac output, which is about 1.2~1.3 liters of blood per minute. The perfusion rate for the kidneys is greater than that for the heart, brain or liver.
  – The perfusion rate is the amount of blood delivered to tissues or organs over a specific period of time.

• The primary functions of the kidneys are to remove metabolic waste from the body and help maintain homeostasis of the kidney.
Storage of Toxic Substances (11)

• Large molecules such as proteins do not easily pass through the walls of Bowman’s capsule.

• The negative charge associated with both albumin and the cell membrane of capillaries repel each other, which further hinders the movement of albumin from the blood into the nephron.

• Once a substance enters the kidneys it may be reabsorbed by either active or passive transport mechanisms along the various parts of the nephron.
Storage of Toxic Substances (12)

• The proximal convoluted tubule is the primary site of reabsorption of water and solutes. Protein, amino acids, glucose molecules, as well as sodium, potassium, and chloride ions are actively transported from the proximal convolute tubule to the peritubular capillaries. Water from the tubule also enters the capillaries as a result of osmosis.

• Active transport mechanisms predominate in the ascending limb of the Loop of Henle. Passive processes exist primarily in the distal convoluted tubule.
Storage of Toxic Substances (13)

• Secretion of various substances from the peritubular capillaries to the nephron can also occur. Ammonia diffuses from the capillaries to the nephron tubules.

• Substances such as hydrogen and potassium ions, as well as penicillin, are actively transported to the lumen of the nephron.
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.
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.
Individual Bone Structure

Compact Bone & Spongy (Cancellous Bone)

- Lacunae containing osteocytes
- Lamellae
- Canaliculi
- Osteon of compact bone
- Trabeculae of spongy bone
- Osteon
- Haversian canal
- Periosteum
- Volkmann's canal
The Nephron of the Kidney
Bowman's Capsule

A - Renal corpuscle
B - Proximal tubule
C - Distal convoluted tubule
D - Juxtaglomerular apparatus
1. Basement membrane (Basal lamina)
2. Bowman's capsule - parietal layer
3. Bowman's capsule - visceral layer
3a. Pedicels (podocyte's)
3b. Podocyte
4. Bowman's space (urinary space)
5a. Mesangium - Intraglomerular cell
5b. Mesangium - Extraglomerular cell
6. Granular cells (Juxtaglomerular cells)
7. Macula densa
8. Miocytes (smooth muscle)
9. Afferent arteriole
10. Glomerulus Capillaries
11. Efferent arteriole
Glomerulus
Human Circulatory System
Hepatic Portal Vein
A Single Lobule of the Liver

- Sinusoid
- Column of liver-cells
- Interlobular vein
- Intralobular vein
- Sublobular vein
Human Liver Sinusoid
The Hepatic Artery

Proper hepatic artery

Common hepatic artery
The Architecture of the Liver

- http://www.youtube.com/watch?v=Gn-ibhGE7PI&feature=related

- The liver is the largest organ in the body. Liver tissue is composed of a compact mass of multisided units, known as the hepatic lobules. Each lobule consists of a central vein, which acts as a tributary of the hepatic vein and conducts processed blood away from the lobule, surrounded by plates of liver cells. The liver receives blood from two sources, 80 percent, which carries digested food materials, arrives from the intestine via the portal vein and venules; the remaining twenty percent is oxygenated blood from the heart, which enters through the hepatic artery and arterioles. An exchange of materials takes place between the liver cells and the blood, which then passes into the central veins and returns to the general body circulation via the hepatic vein. Sinusoids, spaces between plates of liver cells composed of tributaries of the hepatic artery and portal vein, conduct the blood flow to the central vein. The bile canaliculus carries bile juice from the liver to branches of the bile duct which convey bile from the lobules to the gall bladder. When an adult is at rest, about two and a half pints of blood flow through the liver each minute.
Cardiovascular System

• http://www.youtube.com/watch?v=rBQOLiFto6Q&feature=related
General Anatomy of the Liver
Renal Pyramids

1. Renal pyramid
2. Efferent artery
3. Renal artery
4. Renal vein
5. Renal hilum
6. Renal pelvis
7. Ureter
8. Minor calyx
9. Renal capsule
10. Inferior renal capsule
11. Superior renal capsule
12. Afferent vein
13. Nephron
14. Minor calyx
15. Major calyx
16. Renal papilla
17. Renal column
Kidney
Nephron
The Physiology of the Nephron