Chapter 8

Distribution, Storage, and Elimination of Toxicants
Distribution

- Distribution is the process in which a chemical agent, after first gaining entry into the internal body fluid (usually the blood), translocates throughout the fluid compartments of the body.

- The blood carries the toxicant to its sites of biotransformation, site(s) of action, storage, and elimination.
Distribution

• A number of factors can affect the distribution of a toxicant in the body:
  — Lipid solubility
  — Ease of crossing cell membranes
  — Blood flow to the tissue or organ
  — Extent of plasma protein binding
Distribution

• There are a number of concerns regarding the movement and distribution of toxicants throughout the body.

• These concerns involve:
  – the rate of distribution
  – the role of exposure route on distribution outcome
  – the determinants of equal or unequal distribution to the cells and tissues of the body.
Body Water and Volume of Distribution

• The process of toxicant distribution results in the movement of the chemical from the exposure site to internal areas of the body.

• Toxicant distribution depends on many factors, including what is referred to as the apparent volume of distribution ($V_D$)
Apparent Volume of Distribution ($V_D$)

- This concept is related to the concentration of the toxicant in different fluid compartments within the body.
- It is the theoretical total volume of water required to equally distribute the toxicant throughout the body, expressed in liters/kilogram (L/kg).
- This is important to know because it indicates the extent of the distribution of a toxicant within the body fluids.
Body Water and Volume of Distribution

- Water comprises most of the weight of the body and is primarily distributed into three compartments:
  - **Blood plasma water**, simply referred to here as the plasma, accounts for about 4–5% of total body weight.
  - **Interstitial water** is referred to as interstitial fluid, which is the fluid surrounding the cells of the tissues of the body, and represents approximately 15% of total body weight.
  - **Intracellular water**, or intracellular fluid, is a fluid contained within the cells and represents approximately 40% of total body weight (approximately 28 liters of water).
Figure 8-1 Distribution of body water and movement of toxicant between compartments.
Case in Point

A 60-kilogram (kg) individual was exposed to a 1,000-microgram (mcg) dose of a chemical agent that distributed extensively into her body tissues such that only a fraction of the original dose remained within the plasma. The measured plasma concentration of the chemical was 2 micrograms per liter (2 mcg/L); thus it appeared largely distributed into the tissues. It seems that the dose was diluted into a much larger volume of plasma than is actually there.
Case in Point

To account for the entire dose, the 2 mcg/L plasma concentration would require a plasma volume of 1,000 mcg divided by 2 mcg/L, or 500 L. Dividing the volume by body weight, the result is 500 L divided by 60 kg, or 8.33 L/kg. This is the apparent volume of distribution.
Plasma Binding, Blood Flow, and Barriers to Distribution

• A toxicant into the blood will move in the plasma either in the unbound or bound form to be distributed to the tissues and organs of the body.
• The distribution of toxicants from the blood to the tissues and organs of the body may not be uniform.
• Based on specializations of the blood vessels and other factors, certain parts of the body such as the placenta, the testes, and brain may serve as “barriers” to the diffusion of certain chemicals in the blood, thereby restricting their entry and reducing potential toxicity.
Plasma Binding, Blood Flow, and Barriers to Distribution

• These barriers should not be viewed as completely restricting the entry of toxicants; instead, they should be viewed as slowing down the rate of entry.

• Once the toxicant has gained entry into the blood, it can be stored, eliminated, and metabolized.

• Unbound and bound toxicants tend to be in equilibrium in the plasma.
Plasma Binding, Blood Flow, and Barriers to Distribution

• Plasma proteins, especially albumin, may act to bind to the toxicant, thereby reducing its potential to enter the cells of the body, because generally only the unbound toxicant is able to cross cell membranes.

• Plasma protein binding therefore affects the distribution of toxicant, the “effective” dose of the toxicant, and its time within the body.

• Lymph generally plays only a minor role in the distribution of toxicants.
Did You Know?

Integrated $^{109}$Cd K XRF bone-lead measurement is a measure of lead exposure. These have been used to study occupationally exposed workers in many countries along with blood-lead records. Bone-lead levels at bone sites including the sternum, tibia, and calcaneus have correlated with the CBLI. The CBLI is an integrated time-weighted average blood-lead level which corresponds to total lead exposure. The method can therefore provide an accurate measurement of bone-lead level and seems to be a reliable measure of long-term lead exposure.
Toxicant Storage

• The storage of toxicants occurs in connective tissues, primarily fat and bone, and in the kidneys and liver.
  – Fat or adipose tissue is located in many parts of the body and is especially accumulated in the subcutaneous tissue.
  – It is here where lipophilic toxicants are stored and are mobilized back into the blood for further distribution, metabolism, elimination, or redeposition.
Toxicant Storage

• The liver and kidneys, with their relatively high blood flow, may store toxicants in amounts greater than other organs.
• The liver has the greatest capacity of all the tissues for metabolism, which may make it especially vulnerable to injury.
• Bone or osseous tissue is also an important site for the deposition of lead, strontium, and fluoride.
Toxicant Storage, cont.

- Although bone has a relatively poor blood supply, mobilization of elements out of the bone matrix does occur, especially during times of extensive bone remodeling (e.g., repair of a broken bone) or during pregnancy when minerals are mobilized from maternal to fetal compartments.
- For example, lead may be substituted for calcium, and fluoride may be substituted for hydroxyl ions.
- Heavy metals stored in the bone may reside there for decades.
Toxicant Elimination

• The processes of toxicant elimination are critical to the reduction of toxicity or potential toxicity in the body.

• The term *elimination* encompasses all of the processes that are used by the body that lead to a decrease in the amount of toxicant, including
  – Renal elimination
  – Fecal elimination
  – Pulmonary elimination
  – Biotransformation
  – Elimination via minor routes (sweat, milk, nails, etc.)
Case in Point

Vitamin A (retinol), which is required for healthy vision and epithelial tissue, is stored in the liver as a retinol ester and released into the plasma when necessary. Dietary sources of vitamin A can be categorized as preformed vitamin A or provitamin A. Preformed vitamin A is commonly found in animal products such as liver, kidney, and fish oil. Provitamin A is found in leafy green, yellow, and orange vegetables.
Inadequate vitamin A is associated with disparate conditions such as growth retardation, impaired immune function, night blindness, and skin rashes. Vitamin A deficiency is rare in the United States; however, it is a common malady in developing countries. Severe deficiencies can be fatal, particularly in children.
Urinary Excretion

• Elimination of toxicants by renal excretion is one of the most important routes available to the body.
• The kidneys are composed of approximately 1 million functional units referred to as nephrons.
• Each nephron is composed of a capillary ball called a glomerulus and a capsule surrounding the glomerulus (Bowman’s capsule), leading to the proximal tubule, loop of Henle, distal tubule, and, finally, collecting tubule.
Urinary Excretion

• The urinary excretion of toxicant is influenced by factors that are related to the properties of the toxicant:
  – Molecular size
  – Water solubility
  – Degree of ionization
The Nephron & Toxicant Movement

• For most toxicants size is generally not a problem — they are filtered across the glomerulus with relative ease if they are not protein bound in the plasma.

• Ionized toxicants tend to remain within the urine and thus exit when the urine is eliminated from the body.

• Toxicants that are more lipophilic can reenter into the renal circulation through reabsorption, thus increasing their resident time within the body.
Figure 8-3 The nephron and toxicant movement.
Urinary Excretion: Filtration

• The process of toxicant removal from the blood occurs at the glomerulus of the nephron, where a large amount of blood plasma filters through the large pores of the glomerulus and into the beginning of the nephron tube, Bowman’s capsule.
Urinary Excretion: Reabsorption

• Here is where most of the water, electrolytes, amino acids, glucose, and other low-molecular-weight chemicals are returned back to the blood from the glomerular filtrate.

• The process occurs primarily in the proximal convoluted tubule and is driven primarily by simple diffusion.
Urinary Excretion: Secretion

• The process of renal secretion involves the active transport of chemicals from the blood into the proximal tubule of the nephron and is of importance in the conservation of important body ions such as potassium.
Fecal Elimination

• Toxicants can be eliminated in the feces:
  – through their direct discharge into the lumen of the gastrointestinal tract
  – through excretion in the bile
• Toxicants and their metabolites may also be reabsorbed and returned to the liver.
• Biliary excretion is the main route of gastrointestinal elimination of toxicants and their metabolites.
  – Biliary excretion is an active secretory process with specific transporters for organic acids and bases, heavy metals such as lead and mercury, as well as nonionized chemicals.
Fecal Elimination, cont.

• In general, it is the relatively large ionized molecules that are excreted into the bile for elimination.
• Disorders of the liver that may compromise bile secretion could intensify or prolong the effects of some chemicals that would normally be eliminated through this route.
• Toxicants in the bile are transported to the intestinal tract where they are eliminated with the feces or reabsorbed.
Fecal Elimination, cont.

- Excretion of toxicants from the liver generally is accompanied by their biotransformation.
- The enterohepatic circulation is a way in which toxicants can be reabsorbed from the bile that has entered into the gastrointestinal tract at the duodenum and returned to the liver by way of the hepatic portal circulation.
- The recycling of toxicant between intestine and liver has the effect of prolonging its time in the body.
- This is of particular concern because biotransformation in the liver may have produced a metabolite that is more toxic than the parent compound.
Fecal Elimination, cont.

• Toxicants can also be eliminated with the feces through their direct diffusion across the intestinal capillaries of the submucosa to the intestinal lumen where they can be eliminated with the feces.
  
  – Although this relatively slow elimination pathway is not the primary route of toxicant elimination by way of the gastrointestinal tract, it can be important under conditions where urinary or biliary excretion have become less effective.
Pulmonary Elimination

• The lungs have a large surface area and receive the entire cardiac output
• This makes them an important route for the elimination of volatile liquids and gases.
• Important factors that determine elimination of chemicals from the lungs include:
  – concentration differences between alveolar air and blood plasma
  – vapor pressure
  – plasma solubility
Pulmonary Elimination

• Elimination is by simple diffusion from blood to alveolus, following a concentration gradient if the concentration in capillary blood is greater than the concentration of the chemical in the alveolar air.

• For those gases that have a relatively low solubility in blood, elimination is generally much more rapid than for those that are more soluble.
Pulmonary Elimination, cont.

• As an example, chloroform and ethylene are greatly different in their blood solubilities.
• Ethylene does not dissolve well in the blood and is therefore eliminated much more rapidly than chloroform, which has greater blood solubility.
• Lipophilic gases such as halothane have the potential to accumulate in the body’s adipose tissue, and trace amounts in exhaled breath may be present for a long time after the administration of the gas.
Minor Routes of Elimination: Milk

• Toxicants can be transferred from mother’s milk to the nursing infant as well as from cow milk to people.
• Chemicals that are lipophilic are of special concern because milk contains a relatively high percentage of fat
  – these chemicals would diffuse from body fat to plasma to mammary gland and be excreted into milk.
Minor Routes of Elimination: Milk

• Chemicals that behave in the body similar to calcium (e.g., lead) can also be excreted along with calcium into the milk.
• Toxicant transport into milk occurs primarily by diffusion of the nonionized chemical.
• The pH difference between blood plasma and milk, about 7.4 and 6.5, respectively, would favor higher concentrations of organic bases in milk compared with organic acids.
Minor Routes of Elimination, cont.

- **Saliva**: Toxicants that are eliminated to some extent in saliva are usually swallowed, thus prolonging residence time in the body.
- **Sweat**: Some toxicants that are eliminated via sweat may, if present in sufficient quantities, cause skin irritation.
  - **Tears**
  - **Semen**
Minor Routes of Elimination, cont.

• Hair: Although there is negligible elimination via the hair, some chemicals such as mercury and arsenic may be found there using methods that have been developed primarily for forensic purposes.

• Nails: Same as hair

• Eggs (for birds)
  – For some birds, the elimination of toxicants occurs via the eggs.
  – This poses little hazard to the mother but may greatly endanger the young.
Minor Routes of Elimination: Placenta

- The placenta is not traditionally viewed as an excretory organ for toxicants.
- It moves toxicants from maternal compartment to fetal compartment.
  - At the end of a pregnancy, it has a surface area of approximately 10 square meters.
  - It normally functions as an interface, providing oxygen and nutrients to the fetus while eliminating fetal metabolites and carbon dioxide.
  - This occurs by diffusion and active transport.
Minor Routes of Elimination: Placenta

• Maternal elimination of toxicants via the placental route can result in a redistribution of chemicals from maternal tissues to fetal tissues.
• Simple diffusion provides the mechanism to drive lipophilic and low-molecular-weight chemicals across the placenta.
• The placenta is relatively nonprotective to the fetus for lipophilic chemicals, and maternal and fetal tissue levels may be comparable.