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اسم المادة باللغة العربية: السموم العامة

اسم المادة باللغة الإنكليزية: **General toxicology**

المرحلة: الرابعة

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عنوان المحاضرة باللغة العربية: المقدمة (الجزء الثاني)

عنوان المحاضرة باللغة الإنكليزية: **introduction (Part 2)**

ABSORPTION

The process by which toxicants cross body membranes to enter the bloodstream is referred to as absorption. There are no specific systems or pathways for the sole purpose of absorbing toxicants. Xenobiotics penetrate membranes during absorption by the same processes as do biologically essential substances such as oxygen, foodstuffs, and other nutrients. The main sites of absorption are the GI tract, lungs, and skin.

Absorption of Toxicants by the Gastrointestinal Tract

The GI tract is one of the most important sites where toxicants are absorbed. Many environmental toxicants enter the food chain and are absorbed together with food from the GI tract. This site of absorption is also particularly relevant to toxicologists because accidental ingestion is the most common route of unintentional exposure to a toxicant (especially for children) and intentional overdoses most frequently occur via the oral route.

Absorption of toxicants can take place along the entire GI tract, even in the mouth and the rectum. If a toxicant is an organic acid or base, it tends to be absorbed by simple diffusion in the part of the GI tract where it exists in its most lipid-soluble (nonionized) form. Because gastric juice is acidic (pH about 2) and the intestinal contents are nearly neutral, the lipid solubility of weak organic acids or bases can differ markedly in these 2 areas of the GI tract. The Henderson– Hasselbalch equations determine the fraction of a toxicant that is in the nonionized (lipid-soluble) form and estimate the rate of absorption from the stomach or intestine.

However, the Henderson–Hasselbalch calculations are not an absolute determination of absorption because other factors—including the mass action law, surface area, and blood flow rate—have to be taken into consideration in examining the absorption of weak organic acids or bases.

The mammalian GI tract has numerous specialized transport systems (carrier-mediated) for the absorption of nutrients and electrolytes. The absorption of some of these substances is complex and depends on several additional factors. For example, iron absorption is determined by the need for iron and takes place in 2 steps.

Iron accumulates within the mucosal cells as a protein–iron complex termed ferritin. When the concentration of iron in blood drops below normal values, some iron is liberated from the mucosal stores of ferritin and transported into the blood. Calcium is

$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} + \log \frac{[\text{ionized}]}{[\text{nonionized}]}$$

$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} - \log \frac{[\text{nonionized}]}{[\text{ionized}]}$$

also absorbed by a 2-step process: absorption from the lumen followed by exudation into the interstitial fluid. Vitamin D is required for both steps of calcium transport. Some xenobiotics are absorbed by the same specialized transport systems for nutrients, thereby leading to potential competition or interaction. For example, 5-fluorouracil is absorbed by the pyrimidine transport system, thallium utilizes the system that normally absorbs iron, lead can be absorbed by the calcium transporter, and cobalt and manganese compete for the iron transport system.

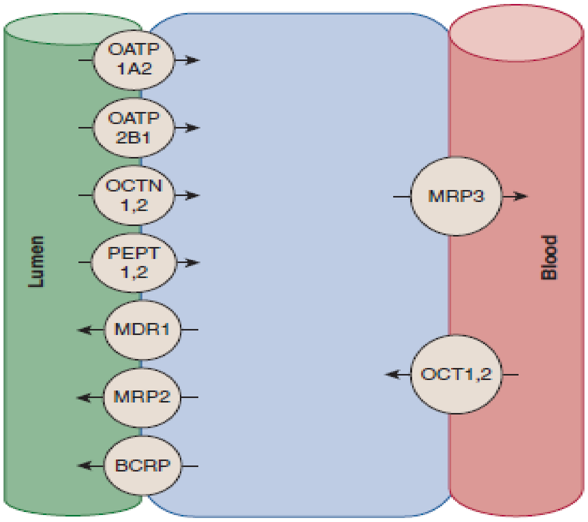
Numerous xenobiotic transporters are expressed in the GI tract where they function to increase or decrease absorption of xenobiotics.
In humans, OATP1A2 and OATP2B1 are the most abundant and important members of this family that are expressed in the intestine, although OATP3A1 and OATP4A1 have also been identified. OCTN1 and OCTN2 are also present in the intestine, with OCTN2 specifically involved in the uptake of carnitine. The peptide transporter, PEPT1 is highly expressed in the GI tract and mediates the transport of peptide-like drugs such as antibiotics, particularly those containing a β-lactam structure. The OCTs, particularly OCT1 and OCT2, also contribute to xenobiotic uptake into enterocytes, but are expressed on the basolateral membrane.

The primary active efflux transporters such as MDR1, MRP2, and BCRP are also expressed on enterocyte brush-border membranes where they function to excrete their substrates into the lumen, thereby decreasing the net absorption of xenobiotics. MRP3 is also found in the intestine, but is localized to the basolateral membrane.

The expression of the intestinal transporters varies across the GI tract. For example, MDR1 expression increases from the duodenum to colon, whereas MRP2 and most of the uptake transporters are expressed most highly in the duodenum and decrease to in the terminal ileum and colon.

Figure: Schematic model showing the important xenobiotic transport systems present in the human gastrointestinal tract.

Particles and particulate matter can also be absorbed by the GI epithelium. In this case, particle size is a major determinant of absorption, whereas factors such as the lipid solubility or ionization characteristics are less important. For particles, size is inversely



related to absorption such that absorption increases with decreasing particle diameter. This explains why metallic mercury is relatively nontoxic when ingested orally and why powdered arsenic was found to be significantly more toxic than its coarse granular form. Large particles (greater than about 20 µm in diameter) enter intestinal cells by pinocytosis, a process that is much more prominent in newborns than in adults. Additionally, surface characteristics of nanoparticles contributes to their absorption, with hydrophobic, nonionized particles being more extensively absorbed than those modified to possess an ionized surface as is the case with larger particles, the gut-associated lymphoid tissue appears to be the predominant absorption pathway for nanoparticles from the GI tract. Overall, the absorption of a toxicant from the GI tract depends on its physical properties, including lipid solubility and its dissolution rate.

In addition to the characteristics of the compounds themselves, there are numerous additional factors relating to the GI tract itself that influence the absorption of xenobiotics. These factors include pH, the presence of food, digestive enzymes, bile acids, and bacterial microflora in the GI tract, along with the motility and permeability of the GI tract. A toxicant may be hydrolyzed by stomach acid, biotransformed by enzymes in the GI tract or modified by the resident microflora to new compounds with a toxicity different from that of the parent compound. For example, snake venoms, which are proteinaceous moieties, are much less toxic by the oral route relative to intravenous exposure because they are degraded by digestive enzymes of the GI tract.

Intestinal microflora can also influence absorption and toxicity of compounds. For example, a variety of nitroaromatic compounds are reduced by intestinal bacteria to potentially toxic and carcinogenic aromatic amines. It has also been shown that ingestion of well water with high nitrate content produces methemoglobinemia much more frequently in infants than in adults. In this case, bacteria in the GI tract convert nitrate to nitrite, increasing the likelihood of methemoglobinemia. Infants are more susceptible to methemoglobinemia because the higher pH of the neonatal GI tract is permissive for the growth of bacteria (such as Escherichia coli) that convert nitrate to nitrite. One example wherein intestinal microflora reduce the potential toxicity is that of the mycotoxin, deoxynivalenol, which is found in numerous grains and foodstuffs. Strict anaerobes detoxify this compound leading to the absorption of a less toxic reductive metabolite. Agents such as the chelator, ethylenediaminetetraacetic acid (EDTA), increase absorption of some toxicants by increasing intestinal permeability. Before a chemical enters the systemic circulation, it can be biotransformed by the cells in the GI tract or extracted by the liver and excreted into bile with or without prior biotransformation. This phenomenon of the removal of chemicals before entrance into the systemic circulation is referred to as presystemic elimination or first-pass effect. Chemicals that have a high first-pass effect will appear to have a lower absorption because they are eliminated as quickly as they are absorbed. Furthermore, metal ions can affect absorption of other ions. For example, cadmium decreases the absorption of zinc and copper, calcium decreases cadmium absorption, and magnesium decreases absorption of fluoride. Consumption of grapefruit juice can also influence GI absorption through the actions of naringin, a flavonoid that inhibits the function of several transporters including MDR1 and OATP1A2. By reducing MDR1-dependent efflux, grapefruit juice increases GI absorption of numerous pharmaceutical agents (such as calcium-channel blockers and cholesterol-lowering agents), and, in some cases, this effect leads to toxic or adverse reactions resulting from increased exposure to the drugs.

Absorption of Toxicants by the Lungs

Toxic responses to chemicals can occur from absorption following inhalation exposure. Relevant examples include carbon monoxide poisoning and silicosis, an important occupational disease. These toxicities result from absorption or deposition of airborne poisons in the lungs. A major group of toxicants that are absorbed by the lungs are gases (eg, carbon monoxide, nitrogen dioxide, and sulfur dioxide), vapors of volatile or volatilizable liquids (eg, benzene and carbon tetrachloride), and aerosols.

Gases and Vapors A vapor is the gas form of substance that can also exist as a liquid or solid at atmospheric pressure and normal temperature. Most organic solvents evaporate and produce vapors, and some solids can also sublimate into a gaseous form. Vapor pressure is that exerted by a vapor above its own liquid in a closed system, such that liquids that have a high vapor pressure have a higher tendency to evaporate. Therefore, the nose acts as a “scrubber” for water-soluble and highly reactive gases. Absorption of gases in the lungs differs from intestinal and percutaneous absorption of compounds in that the dissociation of acids and bases and the lipid solubility of molecules are less important factors in pulmonary absorption because diffusion through cell membranes is not rate-limiting in the pulmonary absorption of gases. At this equilibrium, the ratio of the concentration of chemical in the blood and chemical in the gas phase is constant. This solubility ratio is called the blood-to-gas partition coefficient, and it is unique for each gas.

A gas with a high blood-to-gas partition coefficient, such as chloroform, is readily transferred to blood during each respiratory cycle so that little if any remains in the alveoli just before the next inhalation. The more soluble a toxic chemical is in blood, the more of it will be dissolved in blood by the time equilibrium is reached. With highly soluble gases, the principal factor limiting the rate of absorption is respiration.

AEROSOLS AND PARTICLES

Absorption of aerosol and particles is distinguished from gases and vapors by the factors that determine absorption from the inhalation route of exposure. The absorption of gases and vapors by inhalation is determined by the partitioning of the compound between the blood and the gas phase along with its solubility and tissue reactivity.

In contrast, the important characteristics that affect absorption after exposure to aerosols are the aerosol size and water solubility of any chemical present in the aerosol. The site of deposition of aerosols and particulates depends largely on the size of the particles. Particles ranging from 5 µm or larger, described as "course particles" usually are deposited in the nasopharyngeal region. Particulate matter with diameters of approximately 2.5 μm, referred to as "fine particles" are deposited mainly in the tracheobronchiolar regions of the lungs, from which they may be cleared by retrograde movement of the mucus layer in the ciliated portions of the respiratory tract (also known as the mucociliary escalator).

Particles 1 μm and smaller penetrate to the alveolar sacs of the lungs. Ultrafine- or nanoparticles, particularly those that are approximately 10 to 20 nm in size, have the greatest likelihood of depositing in the alveolar region. These extremely small particles may be absorbed into blood or cleared through the lymphatics after being scavenged by alveolar macrophages.

Absorption of Toxicants through the Skin

Skin is the largest body organ and provides a relatively good barrier for separating organisms from their environment. Overall, human skin comes into contact with many toxic chemicals, but exposure is usually limited by its relatively impermeable nature. However, some chemicals can be absorbed by the skin in sufficient quantities to produce systemic effects. For example, there are several insecticides for which fatal exposures have occurred in agricultural workers after absorption through intact skin. The skin comprises 2 major layers, the epidermis and dermis. The epidermis is the outermost layer and contains keratinocytes that are metabolically competent and able to divide. Ultimately, to be absorbed a chemical must pass the barrier of the stratum corneum and then traverse the other six layers of the skin. In contrast to the complexity of the GI tract, the skin is a simpler penetration barrier for chemicals because passage through the stratum corneum is the rate-determining step. In general, lipophilic (fat-soluble) compounds are absorbed more readily across the stratum corneum, whereas the penetration of hydrophilic (water-soluble) compounds is more limited. although lipophilic compounds may pass more readily through the stratum corneum, their passage through the dermis may become rate-limiting. Hydrophilic compounds are more likely to penetrate the skin through appendages such as hair follicles.

The permeability of the skin also depends on both the diffusivity and the thickness of the stratum corneum. There are several factors that can influence the absorption of toxicants through the skin, including (1) the integrity of the stratum corneum, (2) the hydration state of the stratum corneum, (3) temperature (4) solvents as carriers, and (5) molecular size.

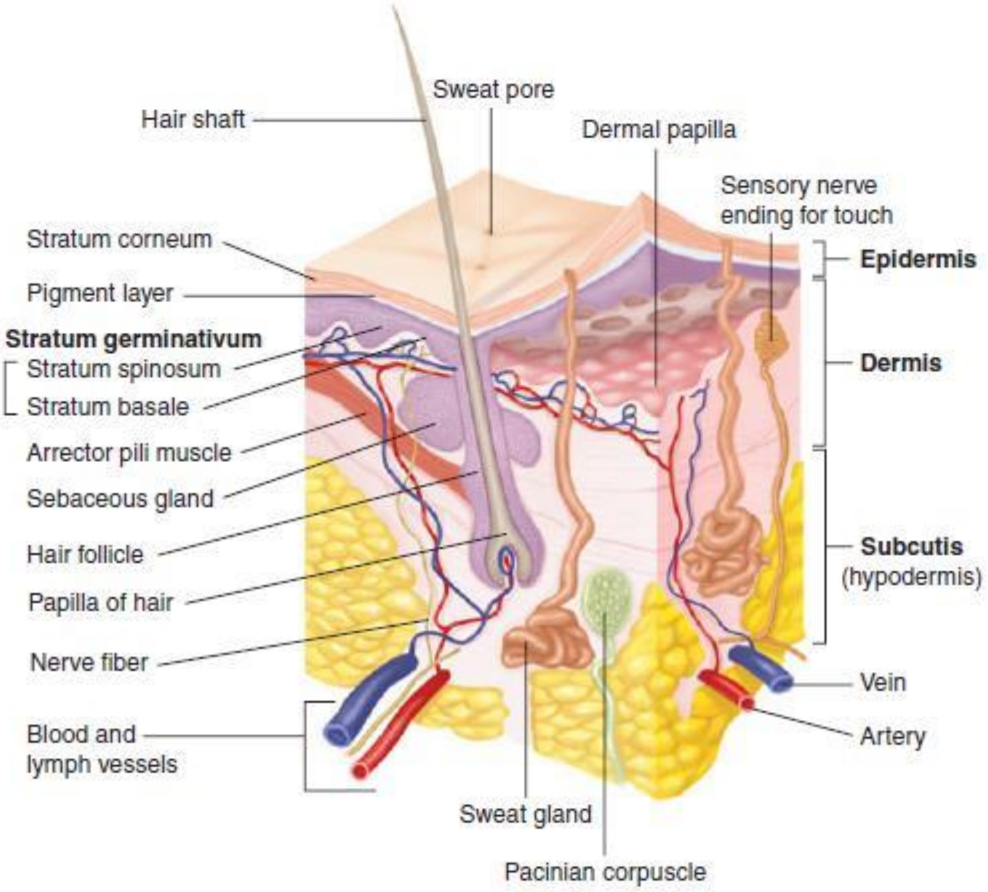


Figure: Diagram of a cross section of human skin illustrating the various layers, cellular composition, and blood supply.

Caustic agents, such as acids and alkalis, that damage the stratum corneum increase its permeability. The most frequently encountered penetration-enhancing damage to the skin results from burns and various skin diseases. Solvents used to dissolve compounds of interest can also influence dermal penetration. In general, lower absorption will be observed if a toxicant is highly soluble in the vehicle, whereas low solubility of the toxicant in the vehicle will tend to increase dermal penetration. In addition, solvents such as dimethyl sulfoxide (DMSO) facilitate the penetration of toxicants through the skin by increasing the permeability of the stratum corneum.

Absorption of Toxicants After Special Routes of Administration The most common routes are (1) intravenous, (2) intraperitoneal, (3) subcutaneous, and (4) intramuscular. The intravenous route introduces the toxicant directly into the bloodstream, eliminating the process of absorption. Intraperitoneal injection results in rapid absorption of xenobiotics because of the rich peritoneal and mesenteric blood supply and the relatively large surface area of the peritoneal cavity. Subcutaneous and intramuscular injections usually result in slower absorption rates, but toxicants enter directly into the general circulation. The rate of absorption by these two routes can be altered by changing the blood flow to the injection site.

If a toxicant is injected intraperitoneally, most of the chemical enters the liver via the portal circulation before reaching the general circulation. Therefore, with intraperitoneal administration, a compound may be completely extracted and biotransformed by the liver with subsequent excretion into bile without gaining access to the systemic circulation. Propranolol and lidocaine are classical examples of drugs with efficient extraction during the first pass through the live.

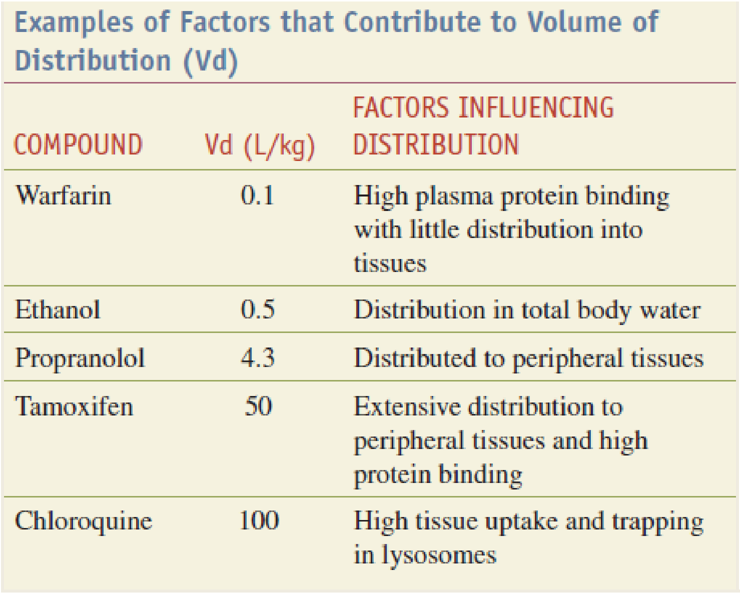
DISTRIBUTION

The rate of distribution to organs or tissues is determined primarily by blood flow and the rate of diffusion out of the capillary bed into the cells of a particular organ or tissue, and usually occurs rapidly.
The final distribution depends largely on the affinity of a xenobiotic for various tissues. In general, the initial phase of distribution is dominated by blood flow, whereas the eventual distribution is determined largely by affinity. The penetration of toxicants into cells occurs by passive diffusion or special transport processes.

Volume of Distribution

A key concept in understanding the disposition of a toxicant is its volume of distribution (Vd), a primary determinant of the concentration of a toxicant in blood that is used to quantify distribution throughout the body. It is defined as the volume in which the amount of drug would need to be uniformly dissolved in order to produce the observed blood concentration.

If a chemical distributes only to the plasma compartment (no tissue distribution), it has a high plasma concentration and hence, a low Vd. In contrast, if a chemical distributes throughout the body (total body water), the effective plasma concentration is low and hence, a high Vd. Some toxicants selectively accumulate in certain parts of the body as a result of protein binding, active transport, or high solubility in fat. In this case, it is assumed that the chemical in the storage depot is toxicologically inactive.



Examples of Factors that Contribute to Volume of Distribution (Vd)

COMPOUND	Vd (L/kg)	FACTORS INFLUENCING DISTRIBUTION
Warfarin	0.1	High plasma protein binding with little distribution into tissues
Ethanol	0.5	Distribution in total body water
Propranolol	4.3	Distributed to peripheral tissues
Tamoxifen	50	Extensive distribution to peripheral tissues and high protein binding
Chloroquine	100	High tissue uptake and trapping in lysosomes

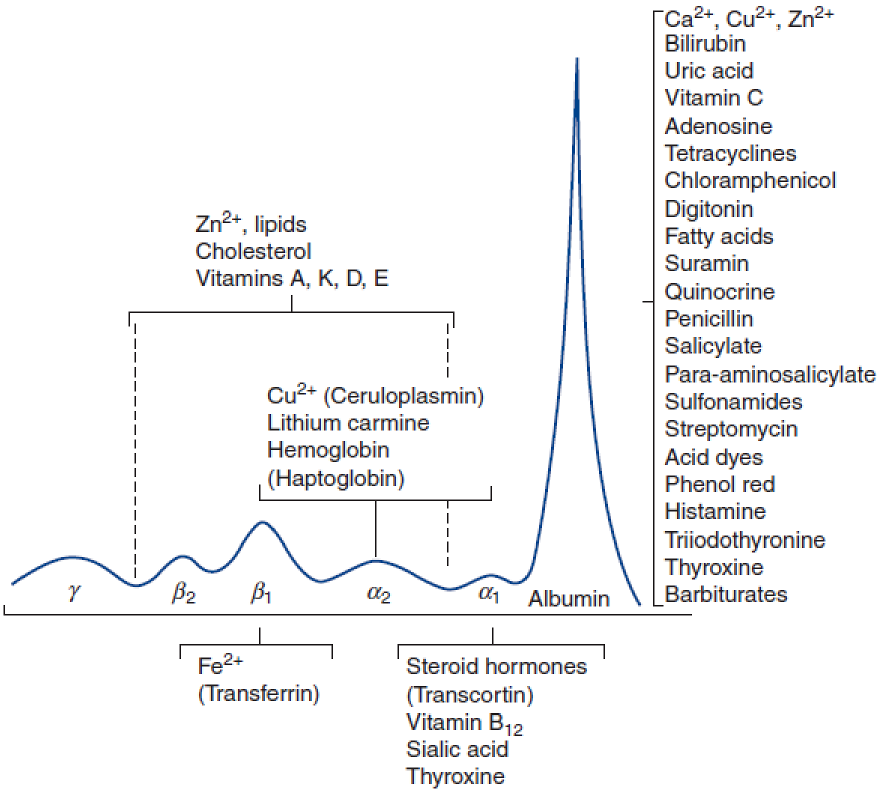
Storage of Toxicants in Tissues

Because only the free fraction of a chemical is in equilibrium throughout the body, binding to or dissolving in certain body constituents greatly alters the distribution of a xenobiotic. The compartment where a toxicant is concentrated is described as a storage depot. Toxicants in these depots are always in equilibrium with the free fraction in plasma.

Plasma Proteins as Storage Depot Binding to plasma proteins is the major site of protein binding, and several different plasma proteins bind xenobiotics and some endogenous constituents of the body. Albumin is the major protein in plasma and it binds many different compounds. α1 -Acid glycoprotein, although present at a much lower concentration than albumin, is also an important protein in plasma, and compounds with basic characteristics tend to bind to it. Transferrin, a β-globulin, is important for the transport of iron in the body. The other major metalbinding protein in plasma is ceruloplasmin, which carries copper.

Figure: Schematic representation of the electrophoretic separation of plasma proteins and xenobiotics that interact with these proteins.

The α- and β-lipoproteins are very important in the transport of lipid-soluble compounds such as vitamins, cholesterol, and steroid hormones as well as xenobiotics. Plasma γ-globulins are antibodies that function specifically in immunological reactions.



Albumin, present in the plasma at a concentration of 500 to 600 μM, is the most abundant protein in plasma and serves as both a depot and multivalent transport protein for many endogenous and exogenous compounds. Protein–ligand interactions occur primarily as a result of hydrophobic forces, hydrogen bonding, and Van der Waals forces. However, the interaction of a chemical with plasma proteins is a reversible process.

In particular, severe toxic reactions can occur if a toxicant with a high degree of protein binding is displaced from plasma proteins by another chemical, increasing the free fraction of the toxicant in plasma. This interaction increases the equilibrium concentration of the toxicant in a target organ, thereby increasing the potential for toxicity. For example, if a compound is 99.9% bound to plasma protein (0.1% free), then an interaction that decreases protein binding to 99.5%, which may seem to be a minor change, is effectively a 5-fold increase in the free plasma concentration (0.5% free). For example, if a strongly bound sulfonamide is given concurrently with an antidiabetic drug, the sulfonamide may displace the antidiabetic drug and induce a hypoglycemic coma. Similarly, interactions resulting from displacement of warfarin can lead to inappropriate blood clotting and possible deleterious effects. Plasma protein binding can also give rise to species differences in the disposition of xenobiotics.

Additional factors that influence plasma protein binding across species include differences in the concentration of albumin, in binding affinity, and/or in competitive binding of endogenous substances.

Liver and Kidney as Storage Depots The liver and kidney have a high capacity for binding many chemicals. These two organs probably concentrate more toxicants than do all the other organs combined, and, in most cases, active transport or binding to tissue components are likely to be involved.

In addition, some proteins serve to sequester xenobiotics in the liver or kidney. For example,
metallothionein (MT), a specialized metal-binding protein, sequesters both essential and toxic metals including zinc and cadmium (Cd) with high affinities in the kidney and liver. Another protein that sequesters certain toxicants in the kidney is α2u-globulin.

Fat as Storage Depot There are many organic compounds that are highly stable and lipophilic, leading to their accumulation in the environment. The lipophilic nature of these compounds also permits rapid penetration of cell membranes and uptake by tissues, and it is not surprising that highly lipophilic toxicants are distributed and concentrated in body fat where they are retained for a very long time. Toxicants appear to accumulate in fat by dissolution in neutral fats, which constitute about 50% and 20% of the body weight of obese individuals and lean athletic individuals, respectively. Storage lowers the concentration of the toxicant in the target organ such that toxicity is likely to be less severe in an obese person than in a lean individual.

Bone as Storage Depot Compounds such as fluoride, lead, and strontium may be incorporated and stored in the bone matrix. For example, 90% of the lead in the body is eventually found in the skeleton.

EXCRETION

Toxicants are eliminated from the body by several routes. The kidney is perhaps the most important organ for the excretion of xenobiotics because more chemicals are eliminated from the body by this route than by any other. Biotransformation to more water-soluble products is usually a prerequisite to the excretion of xenobiotics through urine. The second important route of elimination of many xenobiotics is through feces, and the third, primarily for gases, is through the lungs. Biliary excretion of xenobiotics and/or their metabolites is most often the major source of fecal excretion.

Urinary Excretion

The kidney is a very efficient organ for the elimination of toxicants from the body. Toxic compounds are excreted in urine by the same mechanisms the kidney uses to remove the end products of intermediary metabolism from the body, including glomerular filtration, tubular excretion by passive diffusion, and active tubular secretion. In general, the excretion of small molecular weight (<350 Da), water-soluble compounds is favored in urine.
The kidney receives about 25% of the cardiac output, about 20% of which is filtered at the glomeruli. The glomerular capillaries have large pores (approximately 70 nm), which filter compounds up to a molecular weight of about 60 kDa (smaller than albumin). Thus,

the degree of plasma protein binding affects the rate of glomerular filtration because protein–xenobiotic complexes, particularly those bound to albumin, will not be filtered. A toxicant filtered at the glomerulus may remain in the tubular lumen and be excreted in urine. Depending on the physicochemical properties of a compound, it may be reabsorbed across the tubular cells of the nephron back into the bloodstream. The pH of urine may vary but it is usually slightly acidic (approximately 6–6.5). excretion of salicylate can be accelerated by administering sodium bicarbonate. In a similar manner, urinary acidifycation can be used to increase the excretion of a weak base such as phencyclidine (PCP) in drug abusers.
Toxic agents can also be excreted from plasma into urine by passive diffusion through the tubule.
Xenobiotics can also be excreted into urine by active secretion. This process involves the uptake of toxicants from the blood into the cells of the renal proximal tubule, with subsequent efflux from the cell into the tubular fluid from which urine is formed. Transporters expressed on the basolateral side of the renal tubules in humans that contribute mainly to excretion include OATs, OCTs, and OATP4C1. MDR1, MRP2, and MRP4 are also found on the luminal brush border of the proximal tubule, where they contribute to the efflux of xenobiotics out of the cells and into the tubular fluid, thereby enhancing excretion.

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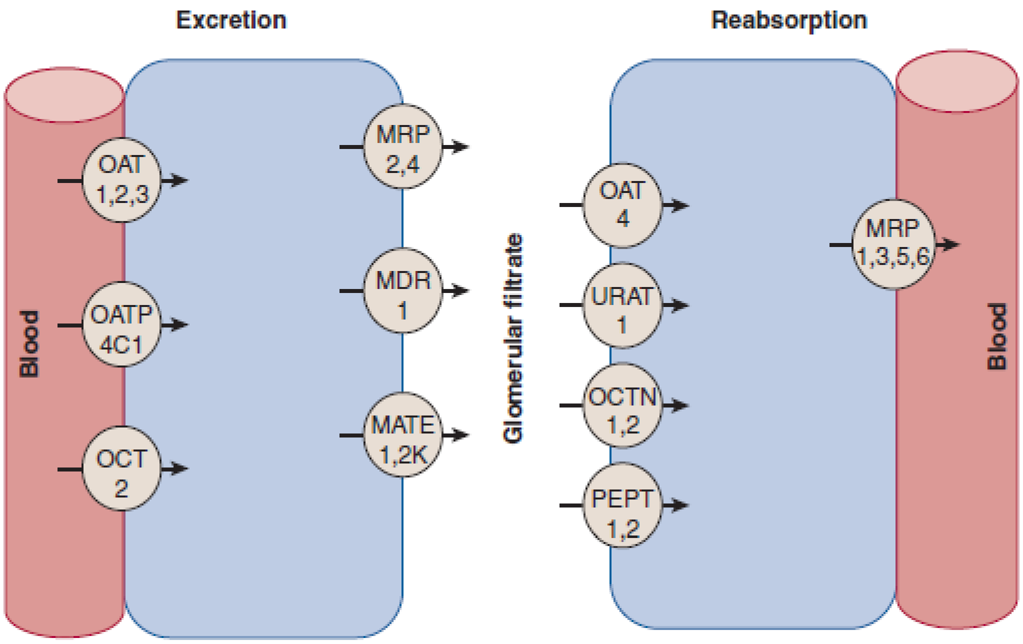

Figure: Schematic model showing the transport systems in the human proximal tubule of the kidney.

As in all active transport systems, there is competition for renal secretion of xenobiotics. This fact was taken advantage of during World War II, when penicillin was in short supply. Penicillin is actively secreted by the organic acid systems (OATs) of the kidney. To lengthen its half-life and duration of action, another acid was sought to compete with penicillin for renal secretion, and probenecid was successfully introduced for this purpose.

Fecal Excretion

Fecal excretion, the second major pathway for the elimination of xenobiotics, is a complex process that is not as well understood as urinary excretion. Excretion of toxicants via the feces can result from direct elimination of nonabsorbed compounds in the GI tract, from delivery to the GI tract via the bile and from secretion into intestinal luminal contents from the enterocytes.

Nonabsorbed Ingesta In addition to undigested material, varying proportions of nutrients and xenobiotics that are present in food or are ingested voluntarily (drugs) pass through the alimentary canal unabsorbed, contributing to fecal excretion.

Biliary Excretion The biliary route of elimination is a significant source contributing to the fecal excretion of xenobiotics and is even more important for the excretion of metabolites. Biliary excretion is regulated predominantly by xenobiotic transporters present on the canalicular membrane, which include MRP2, BCRP, MDR1, MATE1, and BSEP (Fig. 5-13). MRP2 is extremely important in biliary secretion because it is largely responsible for the transport of organic anions including glucuronideand glutathione conjugates of many xenobiotics. BCRP has particular affinity for sulfated conjugates of toxicants, whereas MDR1 primarily transports a variety of substrates into bile. MATE1 is specifically involved in biliary excretion of organic cations, and BSEP is critical for the secretion of bile salts and the regulation of bile flow.

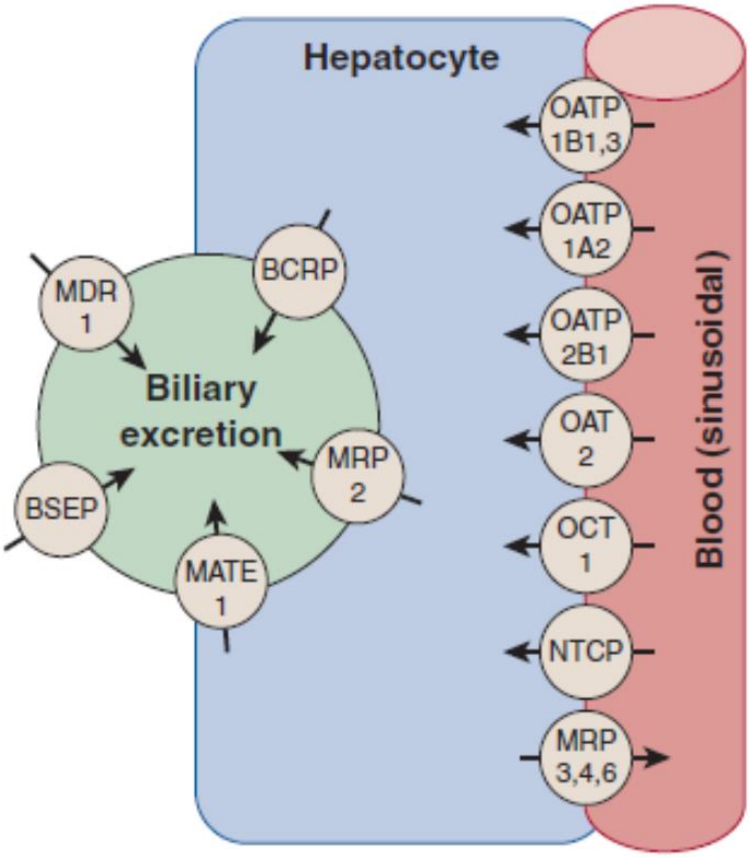

Figure: Schematic model showing the xenobiotic transporting systems present in the human liver.