3 Drug Absorption and Distribution

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Unless a drug acts topically (i.e., at its site of application), it first must enter the bloodstream and then be distributed to its site of action. The mere presence of a drug in the blood, however, does not lead to a pharmacological response. To be effective, the drug must leave the vascular space and enter the intercellular or intracellular spaces or both. The rate at which a drug reaches its site of action depends on two rates: absorption and distribution. *Absorption* is the passage of the drug from its site of administration into the blood; *distribution* is the delivery of the drug to the tissues. To reach its site of action, a drug must cross a number of biological barriers and membranes, predominantly lipid. Competing processes, such as binding to plasma proteins, tissue storage, metabolism, and excretion (Fig. 3.1), determine the amount of drug finally available for interaction with specific receptors.

PROPERTIES OF BIOLOGICAL MEMBRANES THAT INFLUENCE DRUG PASSAGE

Although some substances are translocated by specialized transport mechanisms and small polar compounds may filter through membrane pores, most foreign compounds penetrate cells by diffusing through lipid membranes. A model of membrane structure, shown in Figure 3.2, envisions the membrane as a mosaic structure composed of a discontinuous *bimolecular* lipid layer with fluidlike properties. A smaller component consists of glycoproteins or lipoproteins that are embedded in the lipid matrix and have ionic and polar groups protruding from one or both sides of the membrane. This membrane is thought to be capable of undergoing rapid local shifts, whereby the relative geometry of specific adjacent proteins may change to form channels, or pores. The pores permit the membrane to be less restrictive to the passage of low-molecular-weight hydrophilic substances into cells. In addition to its role as a barrier to solutes, the cell membrane has an important function in providing a structural matrix for a variety of enzymes and drug receptors. The model depicted is *not* thought to apply to capillaries.

Physicochemical Properties of Drugs and the Influence of pH

The ability of a drug to diffuse across membranes is frequently expressed in terms of its lipid–water partition coefficient rather than its lipid solubility per se. This coefficient is defined as the ratio of the concentration of the drug in two immiscible phases: a nonpolar liquid or organic solvent (frequently octanol), representing the membrane; and an aqueous buffer, usually at pH 7.4, representing the plasma. The partition coefficient is a measure of the relative affinity of a drug for the lipid and aqueous phases. Increasing the polarity of a drug, either by increasing its degree of ionization or by adding a carboxyl, hydroxyl, or amino group to the molecule, decreases the lipid–water partition coefficient. Alternatively, reducing drug polarity through suppression of ionization or adding lipophilic (e.g., phenyl or t-butyl) groups results in an increase in the lipid–water partition coefficient.

Drugs, like most organic electrolytes, generally do not completely dissociate (i.e., form ions) in aqueous solution. Only a certain proportion of an organic drug molecule will ionize at a given pH. The smaller the fraction of total drug molecules ionized, the weaker the electrolyte. Since most drugs are either weak organic acids or bases (i.e., weak electrolytes), their degree of

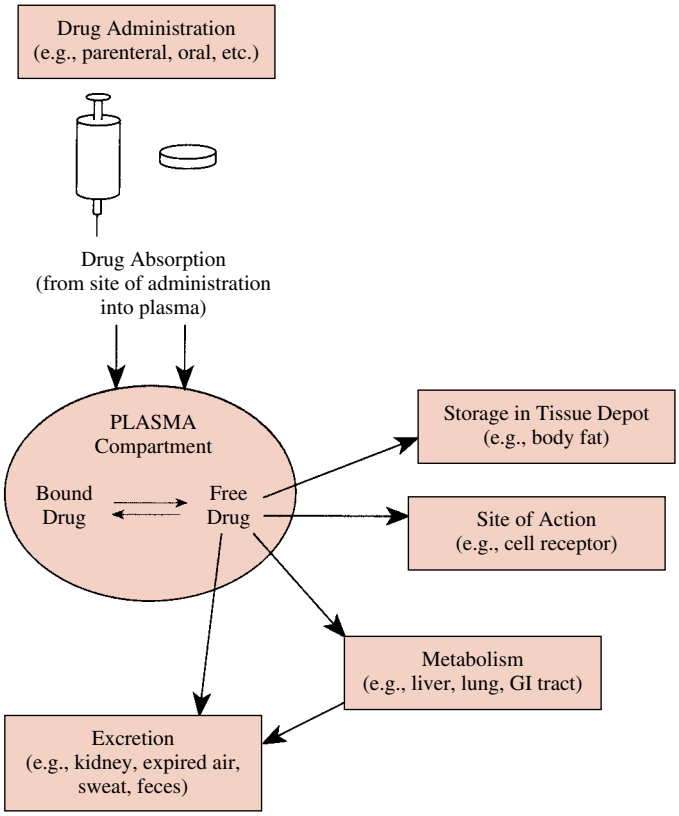

FIGURE 3.1
Factors that affect drug concentration at its site of action. Once a drug has been absorbed into the blood, it may be subjected to varying degrees of metabolism, storage in nontarget tissues, and excretion. The quantitative importance of each of these processes for a given drug determines the ultimate drug concentration achieved at the site of action.

ionization will influence their lipid–water partition coefficient and hence their ability to diffuse through membranes.

The proportion of the total drug concentration that is present in either ionized or un-ionized form is dictated by the drug's dissociation or ionization constant (K) and the local pH of the solution in which the drug is dissolved.

The dissociation of a weak acid, RH, and a weak base, B, is described by the following equations:

$$RH \rightleftharpoons H^+ + R^- \text{ (acid)}$$
$$B + H^+ \rightleftharpoons BH^+ \text{ (base)}$$

If these equations are rewritten in terms of their dissociation constants (using K_a for both weak acids and weak bases), we obtain

$$K_a = \frac{[R^-][H^+]}{[RH]} \text{ (acid)}$$

$$K_a = \frac{[H^+][B\}}{[BH^+]} \text{ (base)}$$

By taking logarithms and then substituting the terms pK and pH for the negative logarithms of K_a and $[H^+]$, respectively, we arrive at the Henderson-Hasselbach equations:

$$pH = pK_a + \log\frac{[R^-]}{[RH]} \text{ (acid)}$$

and

$$pH = pK_a + \log\frac{[B]}{[BH^+]} \text{ (base)}$$

It is customary to describe the dissociation constants of *both* acids and bases in terms of pK_a values. This is possible in aqueous biological systems because a simple mathematical relationship exists between pK_a, pK_b, and the dissociation constant of water pK_w.

$$pK_a + pK_b = pK_w = 14$$
$$pK_a = 14 - pK_b$$

The use of only pK_a values to describe the relative strengths of either weak bases or weak acids makes comparisons between drugs simpler. The lower the pK_a value ($pK_a < 6$) of an acidic drug, the stronger the acid (i.e., the larger the proportion of ionized molecules). The higher the pK_a value ($pK_a > 8$) of a basic drug, the stronger the base. Thus, knowing the pH of the aqueous medium in which the drug is dissolved and the pK_a of the drug, one can, using the Henderson-Hasselbach equation, calculate the relative proportions of ionized and un-ionized drug present in solution. For example, when the pK_a of the drug (e.g., 7) is the same as the pH (e.g., 7) of the surrounding medium, there will be equal proportions of ionized $[R^-]$ and un-ionized [RH] molecules; that is, 50% of the drug is ionized.

The effect of pH on drug ionization is shown in Figure 3.3. The relationship between pH and degree of drug ionization is not linear but sigmoidal; that is, small changes in pH may greatly influence the degree of drug ionization, especially when pH and pK_a values are initially similar.

MECHANISMS OF SOLUTE TRANSPORT ACROSS MEMBRANES

Except for intravenous administration, all routes of drug administration require that the drug be transported from the site of administration into the systemic circulation. A drug is said to be absorbed only when it has entered the blood or lymph capillaries. The transport of drugs across membranes entails one or more of

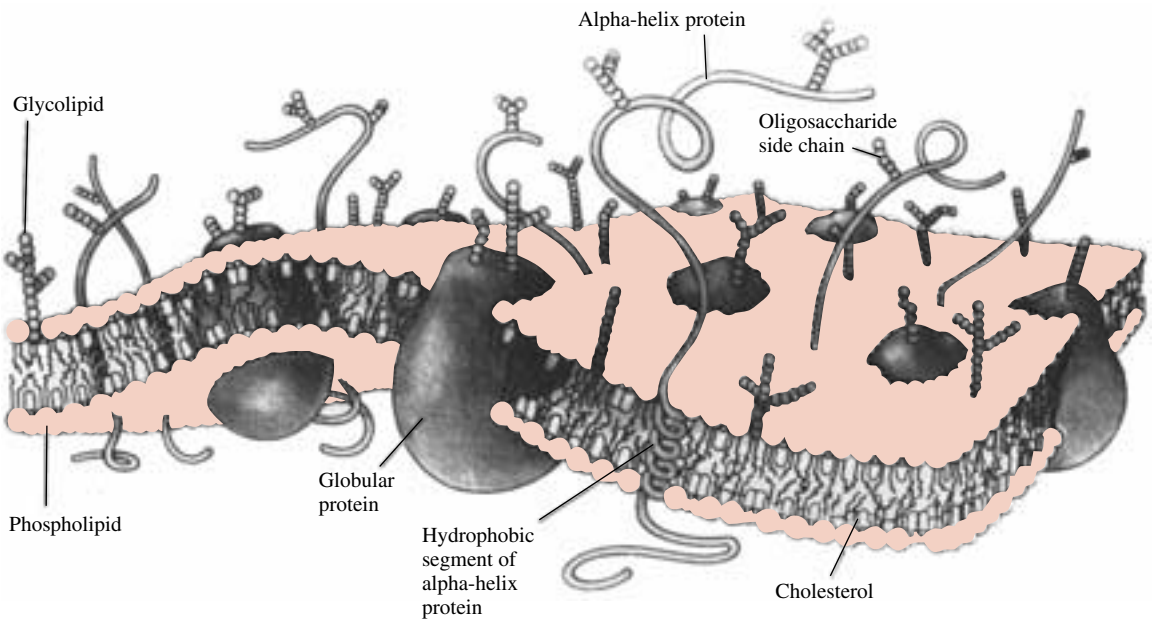

FIGURE 3.2
The plasma membrane, a phospholipid bilayer in which cholesterol and protein molecules are embedded. The bottom layer, which faces the cytoplasm, has a slightly different phospholipid composition from that of the top layer, which faces the external medium. While phospholipid molecules can readily exchange laterally within their own layer, random exchange across the bilayer is rare. Both globular and helical kinds of protein traverse the bilayer. Cholesterol molecules tend to keep the tails of the phospholipids relatively fixed and orderly in the regions closest to the hydrophilic heads; the parts of the tails closer to the core of the membrane move about freely. This model is not believed to apply to blood or lymph capillaries. (Reprinted with permission from Bretscher MS. The molecules of the cell membrane. Sci Am 1985;253:104. Copyright 1985 by Scientific American, Inc. All rights reserved.)

Drug	Intestinal lumen pH 5.0	Membrane barriers	Plasma pH 7.4	Membrane barriers	Stomach pH 1.4
Weak acid—acetaminophen (pK_a 9.5)	[U] = 100 ↓↑ [I] = 0.003 [Total] = 100.003	⇄	[U] = 100 ↓↑ [I] = 0.79 [Total] = 100.79	⇄	[U] = 100 ↓↑ [I] = 0.0 [Total] = 100.0
Weak base—diazepam (pK_a 3.3)	[U] = 100 ↓↑ [I] = 2.0 [Total] = 102.0	⇄	[U] = 100 ↓↑ [I] = 0.008 [Total] = 100.008	⇄	[U] = 100 ↓↑ [I] = 7940.0 [Total] = 8040.0

FIGURE 3.3
Relative concentrations of the weak acid acetaminophen (Pk_a 9.5) and a weak base, diazepam (pK_a 3.3), in some body fluid compartments. [ ], concentration; U, un-ionized drug; I, ionized drug.

the following processes: (1) passive diffusion, (2) filtration, (3) bulk flow, (4) active transport, (5) facilitated transport, (6) ion pair transport, (7) endocytosis, and (8) exocytosis (Fig. 3.4). These processes also participate in the transport of substances necessary for cellular maintenance and growth.

Passive Diffusion

Most drugs pass through membranes by passive diffusion (down their concentration gradient) of the *un-ionized* moiety. The rate of diffusion depends mainly on the lipid–water partition coefficient rather than on lipid solubility per se. For example, the central nervous sys-

tem depressant barbital is almost completely un-ionized at physiological pH and therefore should be able to cross membranes easily. However, barbital's lipid–water partition coefficient is sufficiently low that diffusion across membranes proceeds at an extremely slow rate. This slow rate of passage across central nervous system (CNS) membranes largely explains why the time of onset (*latent period*) of drug action after barbital administration is delayed.

A drug will accumulate in the membrane until the ratio of its concentration in the membrane and its concentration in the extracellular fluid equal its partition coefficient. A concentration gradient is thereby established between the membrane and the intracellular space; this gradient is the driving force for the *passive transfer* of the drug into the cell. Thus, a drug that has a very high lipid–water partition coefficient will have a large concentration gradient, and this favors its rapid diffusion across the membrane and into the cell.

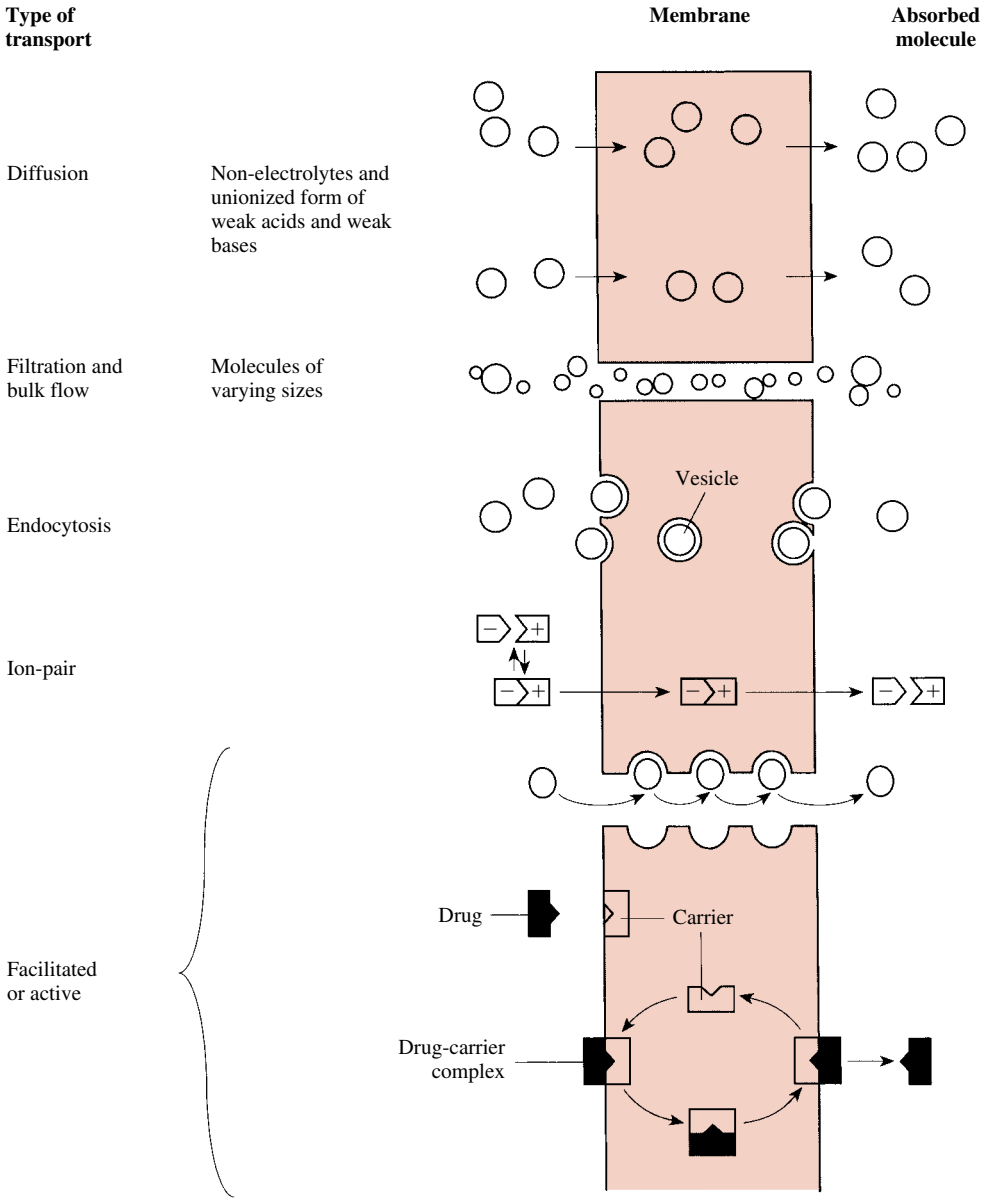

FIGURE 3.4
Mechanisms involved in the passage of drugs across membranes. (Adapted with permission from Smyth DH. Absorption and Distribution of Drugs. Baltimore: Williams & Wilkins, 1964; and Forth W and Rummel W (eds.). Pharmacology of Intestinal Absorption: Gastrointestinal Absorption of Drugs. Vols. 1 and 2. Oxford, UK: Pergammon, 1975).

Filtration

The rate of filtration depends both on the existence of a pressure gradient as a driving force and on the size of the compound relative to the size of the pore through which it is to be filtered. In biological systems, the passage of many small water-soluble solutes through aqueous channels in the membrane is accomplished by filtration. The hypothetical diameter of these pores is about 7 Å, a size that generally limits passage to compounds of molecular weight less than 100 (e.g., urea, ethylene glycol).

Bulk Flow

Most substances, lipid soluble or not, cross the capillary wall at rates that are extremely rapid in comparison with their rates of passage across other body membranes. In fact, the supply of most drugs to the various tissues is limited by blood flow rather than by restraint imposed by the capillary wall. This *bulk flow* of liquid occurs through intercellular pores and is the major mechanism of passage of drugs across most capillary endothelial membranes, with the exception of those in the CNS.

Active Transport

The energy-dependent movement of compounds across membranes, most often against their concentration gradient, is referred to as *active transport.* In general, drugs will not be actively transported unless they sufficiently resemble the endogenous substances (such as sugars, amino acids, nucleic acid precursors) that are the normal substrates for the particular carrier system. This transport involves the reversible binding of the molecule to be transferred to a membrane component (a carrier) of complementary configuration.

Several mechanisms of active transport have been postulated. One transport model proposes that the drug molecule combines with a specific mobile carrier (Fig. 3.4), probably a protein, on one side of the membrane. The complex formed diffuses across the membrane to the opposite side, where the complex dissociates, thus releasing the drug into the aqueous compartment bordering the opposite membrane surface. The carrier protein can then return to its initial side to bind more drug. Another model involves a chainlike arrangement of sites in transport channels to which the drug can bind. The drug would be transferred from one site to another until it had traversed the membrane.

Active transport of a particular substance occurs in one direction only. The number of molecules transported per unit of time will reach a maximum (T_m) once the binding capacity of the carrier becomes saturated. Drugs such as levodopa (for parkinsonism) and α-methyldopa (for hypertension) are actively transported.

Since active transport often requires energy in the form of adenosine triphosphate (ATP), compounds or conditions that inhibit energy production (e.g., iodoacetate, fluoride, cyanide, anaerobiosis) will impair active transport. The transport of a given compound also can be inhibited competitively by the coadministration of other compounds of sufficient structural similarity that they can compete with the first substance for sites on the carrier protein.

Facilitated Diffusion

The transfer of drugs by facilitated diffusion has many of the characteristics associated with active transport, including being a protein carrier–mediated transport system that shows saturability and selectivity. It differs from active transport, however, in that no energy input is required beyond that necessary to maintain normal cellular function. In facilitated transport the movement of the transported molecule is from regions of higher to regions of lower concentrations, so *the driving force for facilitated transport is the concentration gradient.* Although the initial rate of drug transfer will be proportional to the magnitude of the concentration gradient, at some point further increases in drug concentration no longer increase the transport rate; that is, T_m has been reached, since the binding sites on the carrier are now completely saturated.

Ion Pair Transport

Absorption of some highly ionized compounds (e.g., sulfonic acids and quaternary ammonium compounds) from the gastrointestinal tract cannot be explained in terms of the transport mechanisms discussed earlier. These compounds are known to penetrate the lipid membrane despite their low lipid–water partition coefficients. It is postulated that these highly lipophobic drugs combine reversibly with such endogenous compounds as mucin in the gastrointestinal lumen, forming neutral ion pair complexes; it is this neutral complex that penetrates the lipid membrane by passive diffusion.

Endocytosis

Endocytosis involves the cellular uptake of exogenous molecules or complexes inside plasma membrane–derived vesicles. This process can be divided into two major categories: (1) adsorptive or phagocytic uptake of particles that have been bound to the membrane surface and (2) fluid or pinocytotic uptake, in which the particle enters the cell as part of the fluid phase. The solute within the vesicle is released intracellularly, possibly through lysosomal digestion of the vesicle membrane or by intermembrane fusion (Fig. 3.4).

ABSORPTION OF DRUGS FROM THE ALIMENTARY TRACT

Oral Cavity and Sublingual Absorption

In contrast to absorption from the stomach and intestine, drugs absorbed from the oral cavity enter the general circulation directly. Although the surface area of the oral cavity is small, absorption can be rapid if the drug has a high lipid–water partition coefficient and therefore can readily diffuse through lipid membranes. Since the diffusion process is very rapid for un-ionized drugs, pK_a will be a major determinant of the lipid–water partition coefficient for a particular therapeutic agent. For instance, the weak base nicotine (pK_a 8.5) reaches peak blood levels four times faster when absorbed from the mouth (pH 6), where 40 to 50% of the drug is in the un-ionized form, than from the gastrointestinal tract (pH 1–5), where the drug exists mainly in its ionized (protonated) form.

Although the oral mucosa is highly vascularized and its epithelial lining is quite thin, drug absorption from the oral cavity is limited. This is due in part to the relatively slow dissolution rate of most solid dosage forms and in part to the difficulty in keeping dissolved drug in contact with the oral mucosa for a sufficient length of time. These difficulties may be overcome if the drug is placed under the tongue (sublingual administration) or between the cheek and gum (buccal cavity) in a formulation that allows rapid tablet dissolution in salivary secretions. The extensive network of blood vessels facilitates rapid drug absorption. Sublingual administration is the route of choice for a drug like nitroglycerin (glyceryl trinitrate), whose coronary vasodilator effects are required quickly in cases of angina. Furthermore, if swallowed, the drug would be absorbed from the gastrointestinal tract and carried to the liver, where nitroglycerin is subject to rapid metabolism and inactivation.

Absorption from the Stomach

Although *the primary function of the stomach is not absorption,* its rich blood supply and the contact of its contents with the epithelial lining of the gastric mucosa provide a potential site for drug absorption. However, since stomach emptying time can be altered by many variables (e.g., volume of ingested material, type and viscosity of the ingested meal, body position, psychological state), the extent of gastric absorption will vary from patient to patient as well as at different times within a single individual.

The low pH of the gastric contents (pH 1–2) may have consequences for absorption because it can dramatically affect the degree of drug ionization. For example, the weak base diazepam (pK_a 3.3) will be highly protonated in the gastric juice, and consequently, absorption across lipid membranes of the stomach will be particularly slow. On the other hand, the weak acid acetaminophen (pK_a 9.5) will exist mainly in its un-ionized form and can more readily diffuse from the stomach into the systemic circulation (Fig. 3.3).

Because of the influence of pH on ionization of weak bases, basic drugs may be trapped in the stomach even if they are administered intravenously. Since basic compounds exist primarily in their un-ionized form in the blood (pH 7.4), they readily diffuse from the blood into the gastric juice. Once in contact with the gastric contents (pH 1–2), they will ionize rapidly, which restricts their diffusibility. At equilibrium, the concentration of the un-ionized lipid-soluble fraction will be identical on both sides of the gastric membranes, but there will be more *total* basic drug on the side where ionization is greatest (i.e., in gastric contents). This means of drug accumulation is called *ion trapping.*

Absorption from the Small Intestine

The epithelial lining of the small intestine is composed of a single layer of cells called enterocytes. It consists of many villi and microvilli and has a complex supply of blood and lymphatic vessels into which digested food and drugs are absorbed. The small intestine, with its large surface area and high blood perfusion rate, has a greater capacity for absorption than does the stomach. *Most drug absorption occurs in the proximal jejunum* (first 1–2 m in humans).

Although transfer of drugs across the intestinal wall can occur by facilitated transport, active transport, endocytosis, and filtration, the predominant process for most drugs is diffusion. Thus, the pK_a of the drug and the pH of the intestinal fluid (pH 5) will strongly influence the rate of drug absorption. While weak acids like phenobarbital (pK_a 7.4) can be absorbed from the stomach, they are more readily absorbed from the small intestine because of the latter's extensive surface area.

Conditions that shorten intestinal transit time (e.g., diarrhea) decrease intestinal drug absorption, while increases in transit time will enhance intestinal absorption by permitting drugs to remain in contact with the intestinal mucosa longer. Although delays in gastric emptying time will increase gastric drug absorption, in general, *total* drug absorption may actually decrease, since material will not be transferred to the large absorptive surface of the small intestine.

Absorption from the Large Intestine

The large intestine has a considerably smaller absorptive surface area than the small intestine, but it may still serve as a site of drug absorption, especially for compounds that have not been completely absorbed from the small intestine. However, little absorption occurs

from this site, since the relatively solid nature of the intestinal contents impedes diffusion of the *drug* from the contents to the mucosa.

The most distal portion of the large intestine, the rectum, can be used directly as a site of drug administration. This route is especially useful where the drug may cause gastric irritation, after gastrointestinal surgery, during protracted vomiting, and in uncooperative patients (e.g., children) or unconscious ones. Dosage forms include solutions and suppositories. The processes involved in rectal absorption are similar to those described for other sites.

Although the surface area available for absorption is not large, absorption can still occur, owing to the extensive vascularity of the rectal mucosa. Drugs absorbed from the rectum largely escape the biotransformation to which orally administered drugs are subject, because *a portion of the blood that perfuses the rectum is not delivered directly to the liver, and therefore, rectally administered drug, at least in part, escapes hepatic first-pass metabolism.*

FACTORS AFFECTING RATE OF GASTROINTESTINAL ABSORPTION

In addition to the lipid–water partition coefficient of drugs, local blood flow, and intestinal surface area, other factors may affect absorption from the gastrointestinal tract.

Gastric Emptying Time

The rate of gastric emptying markedly influences the rate at which drugs are absorbed, whether they are acids, bases, or neutral substances. In general, factors that accelerate gastric emptying time, thus permitting drugs to reach the large absorptive surface of the small intestine sooner, will increase drug absorption unless the drug is slow to dissolve. A list of physiological, pathological, and pharmacological factors that influence the rate of gastric emptying is provided in Table 3.1.

Intestinal Motility

Increased gastrointestinal motility may facilitate drug absorption by thoroughly mixing intestinal contents and thereby bringing the drug into more intimate contact with the mucosal surface. However, the opposite may also occur in that an increase in motility may reduce contact time in the upper portion of the intestine where most of drug absorption occurs. Conversely, a decrease in gastrointestinal motility may promote absorption by increasing contact time. Thus, the effect depends on the drug and change in motility. Serious intestinal diseases, particularly those associated with intestinal sloughing, can be expected to alter drug absorption dramatically.

Food

Absorption of most drugs from the gastrointestinal tract is reduced or delayed by the presence of food in the gut. Drugs such as the tetracyclines, which are highly ionized, can complex with Ca^{++} ions in membranes, food, or milk, leading to a reduction in their rate of absorption. For drugs that are ionized in the stomach and un-ionized in the intestine, overall absorption will be delayed by any factor that delays gastric emptying. Finally, increased splanchnic blood flow, as occurs during eating, will increase the rate of drug absorption.

Formulation Factors

The ability of solid drug forms to dissolve and the solubility of the individual drug in the highly acidic gastric juice must be considered. For example, although the anticoagulant dicumarol has a very high lipid–water partition coefficient, it precipitates at the low pH of gastric juice, and the rate of its absorption is

TABLE 3.1 Some Factors Influencing Gastric Emptying Time

Factor	Increased gastric emptying rate	Decreased gastric emptying rate
Physiological	Liquids, gastric distention	Solids, acids, fat
Pathological	Duodenal ulcers, gastroenterostomy, chronic pancreatitis	Acute abdominal trauma and pain, labor of child birth, gastric juices, intestinal obstruction, pneumonia, diabetes mellitus
Pharmacological	Reserpine, anticholinesterases, guanethidine, cholinergic agents	Anticholinergic drugs, ganglionic blocking drugs, narcotic analgesics

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thereby reduced. This may be overcome by covering the tablets with an enteric coating that dissolves only in the relatively alkaline secretions in the small intestine. Drugs administered in aqueous solution are absorbed faster and more completely than tablet or suspension forms. Suspensions of fine particles (microcrystalline) are better absorbed than are those of larger particles.

Metabolism and Efflux Transporters

Drugs may be inactivated in the gastrointestinal tract before they are absorbed. Until recently, only gut microflora were implicated in the metabolism of drugs in the gastrointestinal system, affecting drug absorption. However, it has now become apparent that drug-metabolizing enzymes, such as the cytochrome P450 enzymes, play a major role in determining the extent of drug absorption of some drugs. Significant expression of cytochrome P450 3A4 and 3A5 occurs in the enterocytes lining the small intestine. These drug-metabolizing enzymes are responsible for approximately 50% of the cytochrome P450–mediated drug metabolism (see Chapter 4) and thus can be expected to play a major role in the presystemic metabolism of a number of drugs. For example, less than 20% of a dose of the immunosuppressant cyclosporine reaches the systemic circulation intact. In fact, most of the metabolism of cyclosporine prior to reaching the systemic circulation takes place in the gut via cytochrome P450 3A4 and 3A5, not in the liver, as might be expected. Thus, gut metabolism is the major factor responsible for the low percentage of an oral dose of cyclosporine reaching the systemic circulation. Cytochrome P450 2C9 and 2C19 are also expressed in measurable quantities in the human intestine. With any of these four cytochrome P450 enzymes, the variation in expression between individuals is substantial, and so their relative contribution to presystemic metabolism of drugs will vary from person to person.

Recently, it has also been discovered that efflux transporters (transporters that pump drug or substrate out of a cell) are also present in human intestinal enterocytes on the apical side nearest the lumen of the intestine. The predominant transporter protein identified to date is P glycoprotein (Pgp), which is a product of the MDR1 gene. This transporter was originally identified as being overexpressed in tumor cells and responsible in part for multidrug resistance because of its role in the efflux of drugs out of tumor cells; thus the name multidrug resistance (MDR) gene. It has become apparent that many of the drugs that are substrates for cytochrome P450 3A4 are also substrates for Pgp. As a substrate for Pgp, a drug will enter the cell, usually via passive diffusion, but then be picked up by the Pgp transporter and carried back to the gut lumen (efflux). As this continually occurs along the intestine, some of the drug molecules are prevented from being absorbed, which decreases overall absorption. Taken together, the Pgp transporter and the cytochrome P450 enzymes form a mechanism to reduce the amount of drug reaching the systemic circulation.

ABSORPTION OF DRUGS FROM THE LUNG

The lungs serve as a major site of administration for a number of agents given for both local and systemic effects. Such drugs can be inhaled as gases (e.g., volatile anesthetics) or as aerosols (suspended liquid droplets or solid particles). Absorption of agents from the lung is facilitated by the large surface area of the pulmonary alveolar membranes (50–100 m^2), the limited thickness of these membranes (approximately 0.2 μ), and the high blood flow to the alveolar region.

Pulmonary absorption of volatile anesthetics across the alveolar–capillary barrier is very rapid because of the relatively high lipid–water partition coefficients and small molecular radii of such agents. The driving force for diffusion is a combination of the blood–air partition coefficient (which is a measure of the capacity of blood to dissolve drug) and the difference in partial pressure between the alveoli and the arterial and venous blood. Agents with high blood–air partition coefficients require more drug to be dissolved in the blood for equilibrium to be reached.

ABSORPTION OF DRUGS THROUGH THE SKIN

Most drugs that have been incorporated into creams or ointments are applied to the skin for their local effect. The diffusion rate of a drug through the skin is largely determined by the compound's lipid–water partition coefficient. However, the stratum corneum, or outer layer of the epidermis, forms a barrier against the rapid penetration of most drugs. This is due in large part to the relatively close-packed cellular arrangement and decreased amount of lipid in these cells. Thus, even highly lipid-soluble compounds will be absorbed much more slowly through the skin than from other sites. The dermis, on the other hand, is well supplied with blood and lymph capillaries and therefore is permeable to both lipid-soluble and water-soluble compounds. If penetration of the skin by lipid-insoluble compounds does occur, it is probably accomplished by diffusion through the hair follicles, sweat glands, or sebaceous glands.

ABSORPTION OF DRUGS AFTER PARENTERAL ADMINISTRATION

Intramuscular and Subcutaneous Administration

Intramuscular and subcutaneous injections are by far the most common means of parenteral drug administration. Because of the high tissue blood flow and the ability of the injected solution to diffuse laterally, drug absorption generally is more rapid after intramuscular than after subcutaneous injection. Drug absorption from intramuscular and subcutaneous sites depends on the quantity and composition of the connective tissue, the capillary density, and the rate of vascular perfusion of the area. These factors can be influenced by the coinjection of agents that alter local blood flow (e.g., vasoconstrictors or vasodilators) or by substances that decrease tissue resistance to lateral diffusion (e.g., hyaluronidase).

Advantages of the intramuscular and subcutaneous routes include an increased reliability and precision in the drug blood level finally achieved and reasonably rapid absorption and onset of drug action. There are, however, serious disadvantages as well. Pain, tenderness, local tissue necrosis (primarily with highly alkaline injections), microbial contamination, and nerve damage may be associated with these forms of parenteral administration.

Intravenous Administration

Intravenous drug administration ensures immediate pharmacological response; problems of absorption are circumvented because the entire quantity of drug enters the vasculature directly. This route is also useful for compounds that are poorly or erratically absorbed, are extremely irritating to tissues, or are rapidly metabolized before or during their absorption from other sites. The rate of injection should be slow enough, however, to prevent excessively high local drug concentrations and to allow for termination of the injection if undesired effects appear.

A serious disadvantage of intravenous drug administration becomes clearly apparent when an overdose is inadvertently given: Neither can the drug be removed nor its absorption retarded. Other disadvantages include the possibilities of embolism (particularly if an insoluble drug is given), introduction of bacteria, and when this route is used for prolonged periods, subcutaneous tissue infiltration. The possible introduction of the human immunodeficiency virus (HIV) is a well-known consequence of intravenous drug administration in addicts who use contaminated needles.

FACTORS INFLUENCING DRUG DISTRIBUTION

Distribution is the delivery of drug from the systemic circulation to tissues. Once a drug has entered the blood compartment, the *rate* at which it penetrates tissues and other body fluids depends on several factors. These include (1) capillary permeability, (2) blood flow–tissue mass ratio (i.e., perfusion rate), (3) extent of plasma protein and specific organ binding, (4) regional differences in pH, (5) transport mechanisms available, and (6) the permeability characteristics of specific tissue membranes.

Drug delivery and eventual drug equilibration with intercellular tissue spaces are largely determined by the extent of organ blood flow. The composition of the capillary bed is usually not a limiting factor except with the capillaries of the CNS. The renal and hepatic capillaries are especially permeable to the movement of most molecules, except those of particularly large size. The rate of passage of drugs across capillary walls can be influenced by agents that affect capillary permeability (e.g., histamine) or capillary blood flow rate (e.g., norepinephrine).

AVAILABLE DISTRIBUTION VOLUME

The total volume of the fluid compartments of the body into which drugs may be distributed is approximately 40 L in a 70-kg adult. These compartments include plasma water (approximately 10 L), interstitial fluid (10 L), and the intracellular fluid (20 L). Total extracellular water is the sum of the plasma and the interstitial water. Factors such as sex, age, edema, pregnancy, and body fat can influence the volume of these various compartments.

The rate at which an equilibrium concentration of a drug is reached in the extracellular fluid of a particular tissue will depend on the tissue's perfusion rate; the greater the blood flow the more rapid the distribution of the drug from the plasma into the interstitial fluid. Thus, a drug will appear in the interstitial fluid of liver, kidney, and brain more rapidly than it will in muscle and skin (Table 3.2). The pharmacokinetic concept of volume of distribution (a derived parameter that relates the amount of drug in the body to the plasma concentration) is discussed more fully in Chapter 5.

BINDING OF DRUGS TO PLASMA PROTEINS

Most drugs found in the vascular compartment are bound reversibly with one or more of the macromolecules in plasma. Although some drugs simply dissolve in plasma water, most are associated with plasma compo-

TABLE 3.2 Blood Perfusion Rates in Adult Humans

Tissue	Percent of cardiac output	Blood flow (L/min)	Percent of body weight	Perfusion rate (mL/min/100 g tissue)
Kidney	20	1.23	0.5	350
Brain	12	0.75	2.0	55
Lung	100	5.40	1.5	400
Liver	24	1.55	2.8	85
Heart	4	0.25	0.5	84
Muscle	23	0.80	40.0	5
Skin	6	0.40	10.0	5
Adipose tissue	10	0.25	19.0	3

nents such as albumin, globulins, transferrin, ceruloplasmin, glycoproteins, and α- and β-lipoproteins. While many acidic drugs bind principally to albumin, basic drugs frequently bind to other plasma proteins, such as lipoproteins and α_1-acid glycoprotein (α_1-AGP), in addition to albumin. The extent of this binding will influence the drug's distribution and rate of elimination because *only the unbound drug can diffuse through the capillary wall, produce its systemic effects, be metabolized, and be excreted*.

Drugs ordinarily bind to protein in a reversible fashion and in dynamic equilibrium, according to the law of mass action. Since only the unbound (or free) drug diffuses through the capillary walls, extensive binding may decrease the intensity of drug action. The magnitude of this decrease is directly proportional to the fraction of drug bound to plasma protein. At low drug concentrations, the stronger the affinity between the drug and protein, the smaller the fraction that is free. As drug dosage increases, eventually the binding capacity of the protein becomes saturated and any additional drug will remain unbound.

The binding of a drug to plasma proteins will decrease its effective plasma to tissue concentration gradient, that is, the force that drives the drug out of the circulation, thereby slowing the rate of transfer across the capillary. As the free drug leaves the circulation, the protein–drug complex begins to dissociate and more free drug becomes available for diffusion. Thus, binding does not prevent the drug from reaching its site of action but only retards the rate at which this occurs. Extensive plasma protein binding may prolong drug availability and duration of action.

Protein binding also plays a role in the distribution of drugs and thus the volume of distribution. Drugs that are highly bound to plasma proteins may distribute less widely because they remain trapped in the peripheral vasculature, since the plasma proteins themselves cannot traverse into the extravascular space. However, if the affinity of a drug for tissues (e.g., fat, muscle) is greater than the affinity for plasma proteins, widespread distribution can occur despite a high degree of plasma protein binding.

Albumin

Of the plasma proteins, the most important contributor to drug binding is albumin. Although albumin has a *net* negative charge at serum pH, it can interact with both positive and negative charges on drugs. Many highly albumin-bound drugs are poorly soluble in water, and for such drugs, binding to hydrophobic sites on albumin is often important. In general, only one or two molecules of an acidic drug are bound per albumin molecule, whereas basic, positively charged drugs are more weakly bound to a larger number of binding sites.

The binding of drugs to plasma proteins is usually nonspecific; that is, many drugs may interact with the same binding site. A drug with a higher affinity may displace a drug with weaker affinity. Increases in the non–protein-bound drug fraction (i.e., free drug) can theoretically result in an increase in the drug's intensity of pharmacological response, side effects, and potential toxicity. However, in practice, changes in protein binding result in clinically significant effects for only a limited number of drugs.

Some disease states (e.g., hyperalbuminemia, hypoalbuminemia, uremia, hyperbilirubinemia) have been associated with changes in plasma protein binding of drugs. For example, in uremic patients the plasma protein binding of certain acidic drugs (e.g., penicillin, sulfonamides, salicylates, and barbiturates) is reduced.

Lipoproteins

Drugs that bind to lipoproteins do so by dissolving in the lipid portion of the lipoprotein core. The binding

capacity of individual lipoproteins generally depends on their lipid content. It is also possible that the lipid and protein fractions cooperate in the binding process, the drug first binding to a number of sites on the protein moiety and then dissolving in the lipid phase.

α_1-Acid Glycoprotein

The importance of α_1-AGP as a determinant of the plasma protein binding of basic drugs, including the psychotherapeutic drugs chlorpromazine, imipramine, spiroperidol, and nortriptyline, is becoming apparent. There is evidence of increased plasma α_1-AGP levels in certain physiological and pathological conditions, such as injury, stress, surgery, trauma, rheumatoid arthritis, and celiac disease.

SELECTIVE ACCUMULATION OF DRUGS

Drugs will not always be uniformly distributed to and retained by body tissues. The concentrations of some drugs will be either considerably higher or considerably lower in particular tissues than could be predicted on the basis of simple distribution assumptions. This observation is demonstrated in the following examples:

1. *Kidney.* Since the kidneys receive 20 to 25% of the cardiac output, they will be exposed to a relatively large amount of any systemically administered drug. The kidney also contains a protein, metallothionein, that has a high affinity for metals. This protein is responsible for the renal accumulation of cadmium, lead, and mercury.
2. *Eye.* Several drugs have an affinity for the retinal pigment melanin and thus may accumulate in the eye. Chlorpromazine and other phenothiazines bind to melanin and accumulate in the uveal tract, where they may cause retinotoxicity. Chloroquine concentration in the eye can be approximately 100 times that found in the liver.
3. *Fat.* Drugs with extremely high lipid–water partition coefficients have a tendency to accumulate in body fat. However, since blood flow to adipose tissue is low (about 3 mL/100 g/minute), distribution into body fat occurs slowly. Drug accumulation in body fat may result either in decreased therapeutic activity owing to the drug's removal from the circulation or in prolonged activity when only low levels of the drug are needed to produce therapeutic effects. In the latter instance, fat depots provide a slow, sustained release of the active drug. Should body fat be seriously reduced, as during starvation, stored compounds (e.g., DDT and chlordane) may be mobilized, and toxic symptoms may ensue.
4. *Lung.* The lung receives the entire cardiac output; therefore, drug distribution into it is very rapid. Most compounds that accumulate in the lung are basic amines (e.g., antihistamines, imipramine, amphetamine, methadone, phentermine, chlorphentermine, and chlorpromazine) with large lipophilic groups and pK values greater than 8. However, some nonbasic amines, such as the herbicide paraquat, also can accumulate in the lung.
5. *Bone.* Although bone is a relatively inert tissue, it can accumulate such substances as tetracyclines, lead, strontium, and the antitumor agent cisplatin. These substances may accumulate in bone by absorption onto the bone crystal surface and eventually be incorporated into the crystal lattice. Tetracycline deposition during odontogenesis may lead to a permanent yellow-brown discoloration of teeth, dysplasia, and poor bone development. Lead can substitute for calcium in the bone crystal lattice, resulting in bone brittleness. Bone may become a reservoir for the slow release of toxic substances, such as lead and cisplatin.

PHYSIOLOGICAL BARRIERS TO DRUG DISTRIBUTION

Blood-Brain Barrier

The capillary membrane between the plasma and brain cells is much less permeable to water-soluble drugs than is the membrane between plasma and other tissues. Thus, the transfer of drugs into the brain is regulated by the *blood-brain barrier.* To gain access to the brain from the capillary circulation, drugs must pass through cells rather than between them. Only drugs that have a high lipid–water partition coefficient can penetrate the tightly apposed capillary endothelial cells.

Drugs that are partially ionized and only moderately lipid soluble will penetrate at considerably slower rates. Lipid-insoluble or highly ionized drugs will fail to enter the brain in significant amounts. Because the pH of the cerebrospinal fluid is about 7.35, there is some tendency for weak organic bases to concentrate in the cerebrospinal fluid and for weak organic acids to be excluded. In addition, because only the unbound form of a drug is available for diffusion, extensive plasma protein binding also can have dramatic effects on the extent of drug transfer into the brain.

Inflammation, such as occurs in bacterial meningitis or encephalitis, may increase the permeability of the blood-brain barrier, permitting the passage of ionized

lipid-insoluble compounds (e.g., penicillin and ampicillin) that would otherwise be restricted from penetrating into the brain extracellular fluid.

The flow of cerebrospinal fluid is essentially unidirectional; that is, it flows from its site of formation in the choroid plexus through the ventricles to its site of exit at the arachnoid villi. Drugs in this fluid can either enter the brain tissue or be returned to the venous circulation in the *bulk flow* of cerebrospinal fluid carried through the arachnoid villi. Some drugs, such as penicillin, will not leave the cerebrospinal fluid compartment by bulk flow but will be actively transported by the choroid plexus out of the fluid and back into the blood. Finally, drugs may diffuse from brain tissue directly into blood capillaries.

Though drugs appear to cross the blood-brain barrier by passive diffusion, transporter systems in the blood-brain barrier pump drugs back *out* into the systemic circulation. As in the gut, the Pgp transporter system is the primary active transporter in the blood-brain barrier identified to date. This ATP-dependent transporter system picks up substrates that have crossed the capillary endothelial cells and transports them back to the systemic circulation, limiting their penetration into the CNS. Thus, not only are the physicochemical properties of the drug a determinant for penetration into the CNS but penetration also depends on whether the drug is a substrate for the Pgp transporter system.

An important consequence of the existence of a variety of routes of drug removal from the brain is that drugs that slowly penetrate the CNS may never achieve adequate therapeutic brain concentrations. Penicillin, for example, is a less effective antibiotic centrally than it is peripherally.

Placental Barrier

The blood vessels of the fetus and mother are separated by a number of tissue layers that collectively constitute the *placental barrier.* Drugs that traverse this barrier will reach the fetal circulation. The placental barrier, like the blood-brain barrier, does not prevent transport of all drugs but is selective, and factors that regulate passage of drugs through any membrane (e.g., pK_a, lipid solubility, protein binding) are applicable here.

In general, substances that are lipid soluble cross the placenta with relative ease in accordance with their lipid–water partition coefficient and degree of ionization. Highly polar or ionized drugs do not cross the placenta readily. However, most drugs used in labor and delivery are not highly ionized and will cross. They are generally weak bases with pK_a values of about 8 and tend to be more ionized in the fetal bloodstream, since the pH of fetal blood is around 7.3 as compared with the maternal blood pH of 7.44. Differences in maternal and fetal blood pH can give rise to unequal concentrations of ionizable drugs in the mother and the fetus.

Active efflux transporters also exist in the placenta, analogous to the gut and blood-brain barrier. These are Pgp, multidrug resistance–associated protein (MRP), and breast cancer resistance protein (BCRP). These transport proteins are located in many tissues but also appear to be expressed in the placenta. Though the substrate specificities of these proteins have not been completely described, they appear to function as efflux transporters, moving endogenous and exogenous chemicals from the placental cells back to the systemic circulation. In this way, they serve as a mechanism to protect the fetus from exposure to unintended chemicals.

Blood-Testis Barrier

The existence of a barrier between the blood and testes is indicated by the absence of staining in testicular tissue after the intravascular injection of dyes. Morphological studies indicate that the barrier lies beyond the capillary endothelial cells and is most likely to be found at the specialized Sertoli–Sertoli cell junction. It appears that Pgp, the efflux transporter protein, also plays a role in forming this blood-testis barrier. This protein probably plays a role in preventing certain chemotherapeutic agents from reaching specific areas of the testis and thus hinders treatment of the neoplasm.

Study Questions

1. Following oral administration, a drug is absorbed into the body, wherein it can exert its action. For a drug given orally, the primary site of drug absorption is:
(A) The esophagus
(B) The stomach
(C) The upper portion of the small intestine
(D) The large intestine

2. Patients can exhibit alterations in the rate and extent of drug absorption because of various factors. All of the following factors might affect the rate and/or extent of drug absorption EXCEPT:
(A) Gastric emptying time
(B) Intestinal motility
(C) The presence of food
(D) The formulation of the drug
(E) A generic form of the drug

3. The body has developed defense mechanisms that reduce the amount of foreign chemicals, such as drugs, that enter the body. One of the more prominent of these mechanisms is an efflux transport system that pumps some drugs back into the intestinal lumen following absorption into the enterocytes and that is responsible for the lack of complete absorption of some drugs. This efflux transport system is:
   (A) Facilitated diffusion
   (B) P glycoprotein
   (C) Cytochrome P450 3A
   (D) Pinocytosis
4. All of the following statements concerning the blood-brain barrier and the passage of drugs from the systemic circulation into the cerebrospinal fluid are TRUE EXCEPT:
   (A) Ionized drugs are more likely to cross into the CSF than un-ionized drugs.
   (B) The higher the lipid solubility of a drug, the more likely it will cross into the CSF.
   (C) Inflammation of the meninges improves the likelihood that drugs will cross the blood-brain barrier as compared to the uninflamed state (i.e., normal condition).
   (D) P glycoprotein serves to pump drugs back into the systemic circulation from endothelial cells lining the blood-brain barrier.
5. Which of the following organs or tissues is a potential site for drug accumulation of lead that has been ingested?
   (A) Eyes
   (B) Fat
   (C) Bone
   (D) Lungs
   (E) Blood

ANSWERS

1. **C.** The primary site of absorption is the small intestine. Because of its large surface area and high blood perfusion rate, the small intestine is optimal for absorbing drugs. Some drug absorption occurs in the stomach and large intestine, but because of their reduced surface area in relative terms and for some drugs less than optimal physicochemical conditions, these tissues play a lesser role in drug absorption. Because of the tissue type, very little drug absorption occurs through the esophagus.
2. **E.** To be approved, generic formulations must exhibit the same rate and extent of absorption as the trademark compound. All of the other choices can affect drug absorption. For example, slowing gastric emptying time may increase the absorption of a drug absorbed in the stomach. Alterations in gastric motility may affect the amount of time a drug spends in the region of the gastrointestinal tract, where it undergoes the most extensive absorption. The presence of food may cause decreased absorption through binding to the drug or may increase absorption through making a better local environment for absorption of particular drugs. Finally, changes in drug formulation can alter absorption by changing dissolution rates.
3. **B.** P-glycoprotein transporters in the intestinal lumen serve as an efflux transporter for many drugs. This transporter pumps drugs out of the enterocytes into which they were absorbed and back into the intestinal lumen, reducing absorption. Facilitated diffusion and pinocytosis generally result in drug influx (absorption). The cytochrome P450 3A enzymes metabolize drugs; therefore, even though they may reduce the amount of drug absorbed, the reduction is due to drug metabolism, not efflux transport back into the intestinal lumen.
4. **A.** Un-ionized drugs cross into the cerebrospinal fluid more readily than ionized drugs. All of the other choices are correct.
5. **C.** Lead can substitute for calcium in the bone crystal lattice, resulting in bone brittleness. Bone may become a reservoir for other substances as well. Several drugs, such as chlorpromazine, may accumulate in the eye. Drugs with extremely high lipid–water partition coefficients tend to accumulate in fat, while basic amines tend to accumulate in the lungs. Many agents bind avidly to albumin in the blood.

SUPPLEMENTAL READING

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CASE Study Improving Drug Absorption

A 47-year-old man recently received a heart transplant and is being discharged home with oral medications, including cyclosporine. The physician also prescribed diltiazem, a calcium channel blocker used for the treatment of hypertension. Since he did not have hypertension, the patient wondered why this additional drug was being prescribed.

ANSWER: Cyclosporine is an immunosuppressant drug used to prevent transplant rejections. Though an oral formulation is available, it has low bioavailability (very little reaches the systemic circulation as intact drug). Diltiazem will inhibit cytochrome P450 3A4 in the gut. CYP3A4 is the primary enzyme responsible for the presystemic metabolism of cyclosporine and has been implicated as the primary cause for the low amounts of orally administered cyclosporine reaching the systemic circulation. Coadministration of diltiazem greatly increases the bioavailability of cyclosporine, reducing the dose of drug needed. Furthermore, because cyclosporine is relatively expensive, a substantial cost savings is realized. Finally, a common adverse effect of cyclosporine therapy is the development of hypertension, and the diltiazem somewhat protects the patient from this adverse effect.