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TEXTBOOK OF PHARMACOLOGY

药理学

Original Editors

- Bertram G.Katzung
- Joel G.Hardman

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SECTION I
Basic Principles

Chapter 1 Introduction

Pharmacology can be defined as the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes. These substances may be chemicals administered to achieve a beneficial therapeutic effect on some process within the patient or for their toxic effects on regulatory processes in parasites infecting the patient. Such deliberate therapeutic applications may be considered the proper role of **medical pharmacology**, which is often defined as the science of substances used to prevent, diagnose, and treat disease. **Toxicology** is that branch of pharmacology which deals with the undesirable effects of chemicals on living systems, from individual cells to complex ecosystems.

Prehistoric people undoubtedly recognized the beneficial or toxic effects of many plant and animal materials. The earliest written records from China and from Egypt list remedies of many types, including a few still recognized today as useful drugs. Most, however, were worthless or actually harmful. In the 2500 years or so preceding the modern era there were sporadic attempts to introduce rational methods into medicine, but none were successful owing to the dominance of systems of thought that purported to explain all of biology and disease without the need for experimentation and observation. These schools promulgated bizarre notions such as the idea that disease was caused by excesses of bile or blood in the body, that wounds could be healed by applying a salve to the weapon that caused the wound, and so on. Around the end of the 17th century, reliance on observation and experimentation began to replace theorizing in medicine, following the example of the physical sciences. As the value of these methods in the study of disease became clear, physicians in Great Britain and on the Continent began to apply them to the effects of traditional drugs used in their own practices. Thus, materia medica—the science of drug preparation and the medical use of drugs—began to develop as the precursor to pharmacology. However, any understanding of the mechanisms of action of drugs was prevented by the absence of methods for purifying active agents from the crude materials that were available and—even more—by the lack of methods for testing hypotheses about the nature of drug actions. In the late 18th and early 19th centuries, François Magendie and later his student Claude Bernard began to develop the methods of experimental animal physiology and pharmacology. Advances in chemistry and the further development of physiology in the 18th, 19th, and early 20th centuries laid the foundation needed for understanding how drugs work at the organ and tissue levels. Paradoxically, real advances in basic pharmacology during this time were accompanied by an outburst of unscientific promotion by manufacturers and marketers of worthless "patent medicines." It was not until the concepts of rational therapeutics, especially that of the controlled clinical trial, were reintroduced into medicine —about 50 years ago—that it became possible to accurately evaluate therapeutic claims.

Chapter 2 Pharmacokinetics

The Dynamics of Drug Absorption, Distribution, and Elimination

To produce its characteristic effects, a drug must be present in appropriate concentrations at its sites of action. Although obviously a function of the amount of drug administered, the concentrations of active, unbound (free) drug attained also depend upon the extent and rate of its absorption, distribution (which mainly reflects relative binding to plasma and tissue proteins), metabolism (biotransformation), and excretion. These disposition factors are depicted in Figure 2-1 and are described in this chapter.

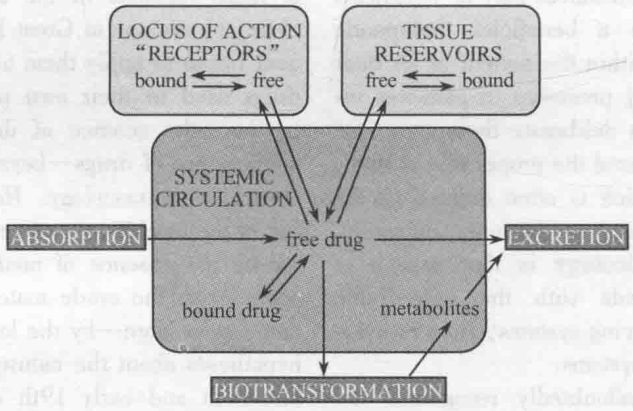

Figure 2-1 Schematic representation of the interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its locus of action.

PHYSICOCHEMICAL FACTORS IN TRANSFER OF DRUGS ACROSS MEMBRANES

The absorption, distribution, metabolism, and excretion of a drug all involve its passage across cell membranes. Mechanisms by which drugs cross membranes and the physicochemical properties of molecules and membranes that influence this transfer are, therefore, important. The determining characteristics of a drug are its molecular size and shape, degree of ionization, relative lipid solubility of its ionized and nonionized forms, and its binding to tissue proteins. When a drug permeates a cell, it obviously must traverse the cellular plasma membrane. Other barriers to drug movement may be a single layer of cells (intestinal epithelium) or several layers of cells (skin). Despite such structural differences, the diffusion and transport of drugs across these various boundaries have many common characteristics, since drugs in general pass through cells rather than between them. The plasma membrane thus represents the common barrier.

Cell Membranes

The plasma membrane consists of a bilayer of amphipathic lipids, with their hydrocarbon chains ori-

ented inward to form a continuous hydrophobic phase and their hydrophilic heads oriented outward. Individual lipid molecules in the bilayer vary according to the particular membrane and can move laterally, endowing the membrane with fluidity, flexibility, high electrical resistance, and relative impermeability to highly polar molecules. Membrane proteins embedded in the bilayer serve as receptors, ion channels, or transporters to elicit electrical or chemical signaling pathways and provide selective targets for drug actions.

Most cell membranes are relatively permeable to water either by diffusion or by flow resulting from hydrostatic or osmotic differences across the membrane, and bulk flow of water can carry with it drug molecules. Such transport is the major mechanism by which drugs pass across most capillary endothelial membranes. However, proteins and drug molecules bound to them are too large and polar for this type of transport to occur; thus, transcapillary movement is limited to unbound drug. Paracellular transport through intercellular gaps is sufficiently large that passage across most capillaries is limited by blood flow and not by other factors (*see* below). As described later, this type of transport is an important factor in filtration across glomerular membranes in the kidney. Important exceptions exist in such capillary diffusion, however, since "tight" intercellular junctions are present in specific tissues and paracellular transport in them is limited. Capillaries of the central nervous system (CNS) and a variety of epithelial tissues have tight junctions (*see* below). Although bulk flow of water can carry with it small, water-soluble substances, if the molecular mass of these compounds is greater than 100 to 200 daltons, such transport is limited. Accordingly, most large lipophilic drugs must pass through the cell membrane itself by one or more processes.

Passive Membrane Transport

Drugs cross membranes either by passive processes or by mechanisms involving the active participation of components of the membrane. In the former, the drug molecule usually penetrates by passive diffusion along a concentration gradient by virtue of its solubility in the lipid bilayer. Such transfer is directly proportional to the magnitude of the concentration gradient across the membrane, the lipid:water partition coefficient of the drug, and the cell surface area. The greater the partition coefficient, the higher is the concentration of drug in the membrane and the faster is its diffusion. After a steady state is attained, the concentration of the unbound drug is the same on both sides of the membrane if the drug is a nonelectrolyte. For ionic compounds, the steady-state concentrations will be dependent on differences in pH across the membrane, which may influence the state of ionization of the molecule on each side of the membrane and on the electrochemical gradient for the ion.

Weak Electrolytes and Influence of PH

Most drugs are weak acids or bases that are present in solution as both the nonionized and ionized species. The nonionized molecules are usually lipid-soluble and can diffuse across the cell membrane. In contrast, the ionized molecules are usually unable to penetrate the lipid membrane because of their low lipid solubility. Therefore, the transmembrane distribution of a weak electrolyte usually is determined by its p*Ka* and the pH gradient across the membrane. The p*Ka* is the pH at which half of the drug (weak electrolyte) is in its ionized form. To illustrate the effect of pH on distribution of drugs, the partitioning of a weak acid (p*Ka* = 4.4) between plasma (pH = 7.4) and gastric juice (pH = 1.4) is depicted in Figure 2-2. It is assumed that the gastric mucosal membrane behaves as a simple lipid barrier that is permeable only to the lipid-soluble, nonionized form of the acid. The ratio of nonionized to ionized drug at each pH is readily calculated from the Henderson-Hasselbalch equation. Thus, in plasma, the ratio of nonionized to ionized drug is 1:1000; in gastric juice, the ratio is 1:0.001. These values are given in brackets in Figure 2-2. The total concentration ratio between the plasma and the gastric juice would therefore be 1000:1 if such a system came to a steady state. For a weak base with a p*Ka* of 4.4, the ratio would be reversed, as would the thick horizontal arrows in Figure 2-2, which indicate the predominant species at each pH. Accordingly, at steady state, an acidic drug will accumulate on the more basic side of the membrane and a basic drug on the more acidic side—a phenomenon termed *ion trapping*. These considerations have obvious implications for the absorption and excretion of drugs, as discussed more specifically below. The establishment of concentration gradients of weak electrolytes

across membranes with a pH gradient is a purely physical process and does not require an active transport system. All that is necessary is a membrane preferentially permeable to one form of the weak electrolyte and a pH gradient across the membrane. The establishment of the pH gradient is, however, an active process.

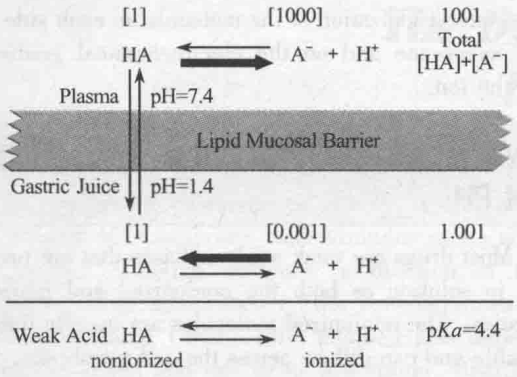

Figure 2-2 Influence of pH on the distribution of a weak acid between plasma and gastric juice, separated by a lipid barrier.

Carrier-Mediated Membrane Transport

While passive diffusion through the bilayer is dominant in the disposition of most drugs, carrier-mediated mechanisms also can play an important role. *Active transport* is characterized by a requirement for energy, movement against an electrochemical gradient, saturability, selectivity, and competitive inhibition by cotransported compounds. The term *facilitated diffusion* describes a carriermediated transport process in which there is no input of energy and therefore enhanced movement of the involved substance is down an electrochemical gradient. Such mechanisms, which may be highly selective for a specific conformational structure of a drug, are involved in the transport of endogenous compounds whose rate of transport by passive diffusion otherwise would be too slow. In other cases, they function as a barrier system to protect cells from potentially toxic substances. The responsible transporter proteins often are expressed within cell membranes in a domain-specific fashion such that they mediate either drug uptake or efflux, and often such an arrangement facilitates vectorial transport across cells. Thus, in the liver, a number of basolaterally localized transporters with different substrate specificities are involved in the uptake of bile acids and amphipathic organic anions and cations into the hepatocyte, and a similar variety of ATP-dependent transporters in the canalicular membrane export such compounds into the bile. Analogous situations also are present in intestinal and renal tubular membranes. An important efflux transporter present at these sites and also in the capillary endothelium of brain capillaries is P-glycoprotein, which is encoded by the multidrug resistance-1 (*MDR1*) gene, important in resistance to cancer chemotherapeutic agents. P-glycoprotein localized in the enterocyte also limits the oral absorption of transported drugs since it exports the compound back into the intestinal tract subsequent to its absorption by passive diffusion.

DRUG ABSORPTION, BIOAVAILABILITY, AND ROUTES OF ADMINISTRATION

Absorption describes the rate at which a drug leaves its site of administration and the extent to which this occurs. However, the clinician is concerned primarily with a parameter designated as *bioavailability*, rather than absorption. *Bioavailability* is a term used to indicate the fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action. For example, a drug given orally must be absorbed first from the stomach and intestine, but this may be limited by the characteristics of the dosage form and/or the drug's physicochemical properties. In addition, drug then passes through the liver, where metabolism and/or biliary excretion may occur before it reaches the systemic circulation. Accordingly, a fraction of the administered and absorbed dose of drug will be inactivated or diverted before it can reach the general circulation and be distributed to its sites of action. If the metabolic or excretory capacity of the liver for the agent in question is large, bioavailability will be substantially reduced (the so-called *first-pass effect*). This decrease in availability is a function of the anatomical site from which absorption takes place; other anatomical, physiological, and pathological factors can influence bioavailability (see below), and the choice of the route of drug administration must be based on an understanding of these conditions.

Oral (Enteral) Versus Parenteral Administration

Often there is a choice of the route by which a therapeutic agent may be given, and a knowledge of the advantages and disadvantages of the different routes of administration is then of primary importance. Some characteristics of the major routes employed for systemic drug effect are compared in Table 2-1. Oral ingestion is the most common method of drug administration. It also is the safest, most convenient, and most economical. Disadvantages to the oral route include limited absorption of some drugs because of their physical characteristics (eg, water solubility), emesis as a result of irritation to the gastrointestinal mucosa, destruction of some drugs by digestive enzymes or low gastric pH, irregularities in absorption or propulsion in the presence of food or other drugs, and necessity for cooperation on the part of the patient. In addition, drugs in the gastrointestinal tract may be metabolized by the enzymes of the intestinal flora, mucosa, or the liver before they gain access to the general circulation. The parenteral injection of drugs has certain distinct advantages over oral administration. In some instances, parenteral administration is essential for the drug to be delivered in its active form. Availability is usually more rapid, extensive, and predictable than when a drug is given by mouth. The effective dose therefore can be more accurately delivered. In emergency therapy and when a patient is unconscious, uncooperative, or unable to retain anything given by mouth, parenteral therapy may be a necessity. The injection of drugs, however, has its disadvantages: asepsis must be maintained; pain may accompany the injection; it is sometimes difficult for patients to perform the injections themselves if self-medication is necessary; and there is the risk of inadvertent administration of a drug when it is not intended. Expense is another consideration.

Oral Ingestion

Absorption from the gastrointestinal tract is governed by factors such as surface area for absorption, blood flow to the site of absorption, the physical state of the drug (solution, suspension, or solid dosage form), its water solubility, and concentration at the site of absorption. For drugs given in solid form, the rate of dissolution may be the limiting factor in their absorption, especially if they have low

Table 2-1 Some Characteristics of Common Routes of Drug Administration

Route	Absorption Pattern	Special utility	Limitation and Precautions
Intravenous	Absorption circumvented Potentially immediate effects	Valuable for emergency use Permits titration of dosage Usually required for high-molecular-weight protein and peptide drugs Suitable for large volumes and for irritating substances, when diluted	Increased risk of adverse effects Must inject solutions *slowly*, as a rule Not suitable for oily solutions or insoluble substances
Subcutaneous	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for some insoluble suspensions and for implantation of solid pellets	Not suitable for large volumes Possible pain or necrosis from irritating substances
Intramuscular	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for moderate volumes, oily vehicles, and some irritating substances	Precluded during anticoagulant medication May interfere with interpretation of certain diagnostic tests (eg, creatine kinase)
Oral ingestion	Variable; depends upon many factors (*see* text)	Most convenient and economical; usually more safe	Requires patient cooperation Availability potentially erratic and incomplete for drugs that are poorly soluble, slowly absorbed, unstable, or extensively metabolized by the liver and/or gut

water solubility. Since most drug absorption from the gastrointestinal tract occurs *via* passive processes, absorption is favored when the drug is in the nonionized and more lipophilic form. Based on the pH-partition concept presented in Figure 2-2, it would be predicted that drugs that are weak acids would be better absorbed from the stomach (pH 1 to 2) than from the upper intestine (pH 3 to 6), and *vice versa* for weak bases. However, the epithelium of the stomach is lined with a thick mucous layer, and its surface area is small; by contrast, the villi of the upper intestine provide an extremely large surface area (~200 m^2). Accordingly, the rate of absorption of a drug from the intestine will be greater than that from the stomach even if the drug is predominantly ionized in the intestine and largely nonionized in the stomach. Thus, any factor that accelerates gastric emptying will be likely to increase the rate of drug absorption, while any factor that delays gastric emptying will probably have the opposite effect, regardless of the characteristics of the drug. Drugs that are destroyed by gastric juice or that cause gastric irritation sometimes are administered in dosage forms with a coating that prevents dissolution in the acidic gastric contents. However, some enteric-coatedpreparations of a drug also may resist dissolution in the intestine, and very little of the drug may be absorbed.

Controlled-Release Preparations

The rate of absorption of a drug administered as a tablet or other solid oral-dosage form is partly dependent upon its rate of dissolution in the gastrointestinal fluids. This factor is the basis for the so-called *controlledrelease*, *extended-release*, *sustained-release*, or *prolonged-action* pharmaceutical preparations that are designed to produce slow, uniform absorption of the drug for 8 hours or longer. Potential advantages of such preparations are reduction in the frequency of administration of the drug as compared with conventional dosage forms (possibly with improved compliance by the patient), maintenance of a therapeutic effect overnight, and decreased incidence and/or intensity of undesired effects by elimination of the peaks in drug concentration that often occur after administration of immediate-release dosage forms. Many controlled-release preparations fulfill these expectations. However, such products have some drawbacks. Generally, interpatient variability, in terms of the systemic concentration of the drug that is achieved, is greater for controlled-release than for immediate-release dosage forms. During repeated drug administration, trough drug concentrations resulting from controlled- release dosage forms may not be different from those observed with immediate-release preparations, although the time interval between trough concentrations is greater for a welldesigned controlled-release product. It is possible that the dosage form may fail, and "dose-dumping" with resultant toxicity can occur, since the total dose of drug ingested at one time may be several times the amount contained in the conventional preparation. Controlled-release dosage forms are most appropriate for drugs with short half-lives (less than 4 hours). So-called controlled-release dosage forms are sometimes developed for drugs with long half-lives (greater than 12 hours). These usually more expensive products should not be prescribed unless specific advantages have been demonstrated.

Sublingual Administration

Absorption from the oral mucosa has special significance for certain drugs, despite the fact that the surface area available is small. For example, nitroglycerin is effective when retained sublingually because it is nonionic and has a very high lipid solubility. Thus, the drug is absorbed very rapidly. Nitroglycerin also is very potent; relatively few molecules need to be absorbed to produce the therapeutic effect. Since venous drainage from the mouth is to the superior vena cava, the drug also is protected from rapid hepatic first-pass metabolism, which is sufficient to prevent the appearance of any active nitroglycerin in the systemic circulation if the sublingual tablet is swallowed.

Rectal Administration

The rectal route often is useful when oral ingestion is precluded because the patient is unconscious or when vomiting is present—a situation particularly relevant to young children. Approximately 50% of the drug that is absorbed from the rectum will bypass the liver; the potential for hepatic first-pass metabolism is thus less than that for an oral dose. However, rectal absorption often is irregular and incomplete, and many drugs cause irritation of the rectal mucosa.

Parenteral Injection

The major routes of parenteral administration are intravenous, subcutaneous, and intramuscular. Absorption from subcutaneous and intramuscular sites occurs by simple diffusion along the gradient from drug depot to plasma. The rate is limited by the area of the absorbing capillary membranes and by the solubility of the substance in the interstitial fluid. Relatively large aqueous channels in the endothelial membrane account for the indiscriminate diffusion of molecules regardless of their lipid solubility. Larger molecules, such as proteins, slowly gain access to the circulation by way of lymphatic channels. Drugs administered into the systemic circulation by any route, excluding the intraarterial route, are subject to possible first-pass elimination in the lung prior to distribution to the rest of the body. The lungs serve as a temporary storage site for a number of agents, especially drugs that are weak bases and are predominantly nonionized at the blood pH, apparently by their partition into lipid. The lungs also serve as a filter for particulate matter that may be given intravenously, and, of course, they provide a route of elimination for volatile substances.

Intravenous

Factors relevant to absorption are circumvented by intravenous injection of drugs in aqueous solution, because bioavailability is complete and rapid. Also, drug delivery is controlled and achieved with an accuracy and immediacy not possible by any other procedure. In some instances, as in the induction of surgical anesthesia, the dose of a drug is not predetermined but is adjusted to the response of the patient. Also, certain irritating solutions can be given only in this manner, since the blood vessel walls are relatively insensitive, and the drug, if injected slowly, is greatly diluted by the blood.

As there are advantages to the use of this route of administration, so are there liabilities. Unfavorable reactions are likely to occur, since high concentrations of drug may be attained rapidly in both plasma and tissues. Because of this, it is advisable to intravenously administer a drug slowly by infusion rather than by rapid injection, and with close monitoring of the patient's response. Furthermore, once the drug is injected there is no retreat. Repeated intravenous injections are dependent upon the ability to maintain a patent vein. Drugs in an oily vehicle or those that precipitate blood constituents or hemolyze erythrocytes should not be given by this route.

Topical Application

Mucous Membranes

Drugs are applied to the mucous membranes of the conjunctiva, nasopharynx, oropharynx, vagina, colon, urethra, and urinary bladder primarily for their local effects. Occasionally, as in the application of synthetic antidiuretic hormone to the nasal mucosa, systemic absorption is the goal. Absorption through mucous membranes occurs readily. In fact, local anesthetics applied for local effect sometimes may be absorbed so rapidly that they produce systemic toxicity.

Skin

Few drugs readily penetrate the intact skin. Absorption of those that do is dependent on the surface area over which they are applied and to their lipid solubility, since the epidermis behaves as a lipid barrier . The dermis, however, is freely permeable to many solutes; consequently, systemic absorption of drugs occurs much more readily through abraded, burned, or denuded skin. Inflammation and other conditions that increase cutaneous blood flow also enhance absorption. Toxic effects sometimes are produced by absorption through the skin of highly lipid-soluble substances (eg, a lipid-soluble insecticide in an organic solvent). Absorption through the skin can be enhanced by suspending the drug in an oily vehicle and rubbing the resulting preparation into the skin. Because hydrated skin is more permeable than dry skin, the dosage form may be modified or an occlusive dressing may be used to facilitate absorption. Controlled-release topical patches are becoming increasingly available. A patch containing scopolamine, placed behind the ear where body temperature and blood flow enhance absorption, releases sufficient drug to the systemic circulation to protect the wearer from motion sickness. Transdermal estrogen replacement therapy yields low maintenance levels of estradiol while minimizing the high estrone metabolite levels observed following oral administration.

Eye

Topically applied ophthalmic drugs are used primarily for their local effects. Systemic absorption that results from drainage through the nasolacrimal canal is usually undesirable. In addition, drug that is absorbed after such drainage is not subject to

first-pass hepatic elimination. Unwanted systemic pharmacological effects may occur for this reason when β-adrenergic receptor antagonists are administered as ophthalmic drops. Local effects usually require absorption of the drug through the cornea; corneal infection or trauma thus may result in more rapid absorption. Ophthalmic delivery systems that provide prolonged duration of action (eg, suspensions and ointments) are useful additions to ophthalmic therapy. Ocular inserts, developed more recently, provide continuous delivery of low amounts of drug. Very little is lost through drainage; hence, systemic side effects are minimized.

DISTRIBUTION OF DRUGS

Following absorption or administration into the systemic blood, a drug distributes into interstitial and intracellular fluids. This process reflects a number of physiological factors and the particular physicochemical properties of the individual drug. Cardiac output, regional blood flow, and tissue volume determine the rate of delivery and potential amount of drug distributed into tissues. Initially, liver, kidney, brain, and other well-perfused organs receive most of the drug, whereas delivery to muscle, most viscera, skin, and fat is slower. This second distribution phase may require minutes to several hours before the concentration of drug in tissue is in distribution equilibrium with that in blood. The second phase also involves a far larger fraction of body mass than does the initial phase and generally accounts for most of the extravascularly distributed drug. With exceptions such as the brain, diffusion of drug into the interstitial fluid occurs rapidly because of the highly permeable nature of the capillary endothelial membrane. Thus, tissue distribution is determined by the partitioning of drug between blood and the particular tissue. Lipid solubility is an important determinant of such uptake as is any pH gradient between intracellular and extracellular fluids for drugs that are either weak acids or bases. However, in general, ion trapping associated with the latter factor is not large, since the pH difference (7.0 *versus* 7.4) is small. The more important determinant of blood:tissue partitioning is the relative binding of drug to plasma proteins and tissue macromolecules.

Plasma Proteins

Many drugs are bound to plasma proteins, mostly to plasma albumin for acidic drugs and to α_1-acid glycoprotein for basic drugs; binding to other plasma proteins generally occurs to a much smaller extent. The binding is usually reversible; covalent binding of reactive drugs such as alkylating agents occurs occasionally.

The fraction of total drug in plasma that is bound is determined by the drug concentration, its affinity for the binding sites, and the number of binding sites. Simple mass-action relationships determine the unbound and bound concentrations. At low concentrations of drug (less than the plasma-protein binding dissociation constant), the fraction bound is a function of the concentration of binding sites and the dissociation constant. At high drug concentrations (greater than the dissociation constant), the fraction bound is a function of the number of binding sites and the drug concentration. Therefore, plasma binding is a saturable and nonlinear process. For most drugs, however, the therapeutic range of plasma concentrations is limited; thus, the extent of binding and the unbound fraction is relatively constant. The percentage values listed in Appendix II refer only to this situation unless otherwise indicated. The extent of plasma binding also may be affected by disease-related factors. For example, hypoalbuminemia secondary to severe liver disease or the nephrotic syndrome results in reduced binding and an increase in the unbound fraction. Also, conditions resulting in the acute phase reaction response (cancer, arthritis, myocardial infarction, Crohn's disease) lead to elevated levels of α_1-acid glycoprotein and enhanced binding of basic drugs.

Because binding of drugs to plasma proteins is rather nonselective, many drugs with similar physicochemical characteristics can compete with each other and with endogenous substances for these binding sites. For example, displacement of unconjugated bilirubin from binding to albumin by the sulfonamides and other organic anions is known to increase the risk of bilirubin encephalopathy in the newborn. Concern for drug toxicities based on a similar competition between drugs for binding sites has, in the past, been overemphasized. Since drug responses, both efficacious and toxic, are a function of unbound concentrations, steady-state unbound concentrations will change only when either drug input (dosing rate) or clearance of unbound drug is changed [see Equation (2-1) and discussion later in this chapter]. Thus, steady-state unbound concentrations are independent of the extent of protein

binding. However, for narrow-therapeutic-index drugs, a transient change in unbound concentrations occurring immediately following the dose of a displacing drug could be of concern. A more common problem resulting from competition of drugs for plasma-protein binding sites is misinterpretation of measured concentrations of drugs in plasma, since most assays do not distinguish free drug from bound drug.

Importantly, binding of a drug to plasma proteins limits its concentration in tissues and at its locus of action, since only unbound drug is in equilibrium across membranes. Accordingly, after distribution equilibrium is achieved, the concentration of active, unbound drug in intracellular water is the same as that in plasma except when carrier-mediated transport is involved. Binding also limits glomerular filtration of the drug, since this process does not immediately change the concentration of free drug in the plasma (water is also filtered). However, plasmaprotein binding generally does not limit renal tubular secretion or biotransformation, since these processes lower the free drug concentration, and this is rapidly followed by dissociation of the drug-protein complex. Drug transport and metabolism also are limited by plasma binding except when these are especially efficient and drug clearance, calculated on the basis of unbound drug, exceeds organ plasma flow. In this situation, binding of the drug to plasma protein may be viewed as a transport mechanism that fosters drug elimination by delivering drug to sites for elimination.

Tissue Binding

Many drugs accumulate in tissues at higher concentrations than those in the extracellular fluids and blood. For example, during long-term administration of the antimalarial agent quinacrine, the concentration of drug in the liver may be several thousandfold higher than that in the blood. Such accumulation may be a result of active transport or, more commonly, binding. Tissue binding of drugs usually occurs with cellular constituents such as proteins, phospholipids, or nuclear proteins and generally is reversible. A large fraction of drug in the body may be bound in this fashion and serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation.

Fat as a Reservoir

Many lipid-soluble drugs are stored by physical solution in the neutral fat. In obese persons, the fat content of the body may be as high as 50%, and even in starvation it constitutes 10% of body weight; hence, fat can serve as an important reservoir for lipid-soluble drugs. For example, as much as 70% of the highly lipid-soluble barbiturate thiopental may be present in body fat 3 hours after administration. However, fat is a rather stable reservoir because it has a relatively low blood flow.

Bone

The tetracycline antibiotics (and other divalent-metalion chelating agents) and heavy metals may accumulate in bone by adsorption onto the bone-crystal surface and eventual incorporation into the crystal lattice. Bone can become a reservoir for the slow release of toxic agents such as lead or radium into the blood; their effects can thus persist long after exposure has ceased. Local destruction of the bone medulla also may lead to reduced blood flow and prolongation of the reservoir effect, since the toxic agent becomes sealed off from the circulation; this may further enhance the direct local damage to the bone. A vicious cycle results, whereby the greater the exposure to the toxic agent, the slower is its rate of elimination.

Redistribution

Termination of drug effect usually is by metabolism and excretion, but it also may result from redistribution of the drug from its site of action into other tissues or sites. Redistribution is a factor in terminating drug effect primarily when a highly lipid-soluble drug that acts on the brain or cardiovascular system is administered rapidly by intravenous injection or by inhalation. A good example of this is the use of the intravenous anesthetic thiopental, a highly lipid-soluble drug. Because blood flow to the brain is so high, the drug reaches its maximal concentration in brain within a minute after it is injected intravenously. After injection is concluded, the plasma concentration falls as thiopental diffuses into other tissues, such as muscle. The concentration of the drug in brain follows that of the plasma, because there is little binding of the drug to brain constituents. Thus, onset of anesthesia is rapid, but so is its termination. Both are directly related to the con-

centration of drug in the brain.

Central Nervous System and Cerebrospinal Fluid

The distribution of drugs into the CNS from the blood is unique, because functional barriers are present that restrict entry of drugs into this critical site. One reason for this is that the brain capillary endothelial cells have continuous tight junctions; therefore, drug penetration into the brain depends on transcellular rather than paracellular transport between cells. The unique characteristics of pericapillary glial cells also contribute to the blood-brain barrier. At the choroid plexus, a similar blood-cerebrospinal fluid (CSF) barrier is present except that it is epithelial cells that are joined by tight junctions rather than endothelial cells. As a result, the lipid solubility of the nonionized and unbound species of the drug is an important determinant of its uptake by the brain; the more lipophilic it is, the more likely it is to cross the blood-brain barrier. This situation often is used in drug design to alter brain distribution; for example, nonsedating antihistamines achieve far lower brain concentrations than do other agents in this class. Increasing evidence also indicates that drugs may penetrate into the CNS by specific uptake transporters normally involved in the transport of nutrients and endogenous compounds from blood into the brain and CSF. Recently, it has been discovered that another important factor in the functional blood-brain barrier also involves membrane transporters which are, in this case, efflux carriers present in the brain capillary endothelial cell. P-glycoprotein is the most important of these and functions by a combination of not allowing drug to even translocate across the endothelial cell and also by exporting any drug that enters the brain by other means. Such transport may account for the brain, and other tissues where P-glycoprotein is similarly expressed (eg, the testes), being pharmacological sanctuary sites where drug concentrations are below those necessary to achieve a desired effect even though blood levels are adequate. This situation apparently occurs with HIV protease inhibitors (Kim et al, 1998) and also with loperamide—a potent, systemically active opioid that lacks any central effects characteristic of other opioids. Efflux transporters that actively secrete drug from the CSF into the blood also are present in the choroid plexus. Regardless of whether a drug is pumped out of the CNS by specific transporters or diffuses back into the blood, drugs also exit the CNS along with the bulk flow of CSF through the arachnoid villi. In general, the blood-brain barrier's function is well maintained; however, meningeal and encephalic inflammation increase the local permeability. There also is the potential that the blood-brain barrier may be advantageously modulated to enhance the treatment of infections or tumors in the brain. To date, however, such an approach has not been shown to be clinically useful.

Placental Transfer of Drugs

The potential transfer of drugs across the placenta is important, since drugs may cause congenital anomalies. Administered immediately before delivery, they also may have adverse effects on the neonate. Lipid solubility, extent of plasma binding, and degree of ionization of weak acids and bases are important general determinants, as previously discussed. The fetal plasma is slightly more acidic than that of the mother (pH 7.0 to 7.2 *versus* 7.4), so that ion-trapping of basic drugs occurs. As in the brain, P-glycoprotein is present in the placenta and functions as an export transporter to limit fetal exposure to potentially toxic agents. But the view that the placenta is an absolute barrier to drugs is inaccurate. A more appropriate approximation is that the fetus is to at least some extent exposed to essentially all drugs taken by the mother.

EXCRETION OF DRUGS

Drugs are eliminated from the body either unchanged by the process of excretion or converted to metabolites. Excretory organs, the lung excluded, eliminate polar compounds more efficiently than substances with high lipid solubility. Lipid-soluble drugs thus are not readily eliminated until they are metabolized to more polar compounds.

The kidney is the most important organ for excreting drugs and their metabolites. Substances excreted in the feces are mainly unabsorbed, orally ingested drugs or metabolites excreted either in the bile or secreted directly into the intestinal tract and, subsequently, not reabsorbed. Excretion of drugs in breast milk is important, not because of the amounts eliminated, but because the excreted drugs are potential sources of unwanted pharmacological effects in the nursing infant. Pulmonary excretion is important mainly for the elimination of anesthetic gases

and vapors; occasionally, small quantities of other drugs or metabolites are excreted by this route.

Renal Excretion

Excretion of drugs and metabolites in the urine involves three processes: glomerular filtration, active tubular secretion, and passive tubular reabsorption. Changes in overall renal function generally affect all three processes to a similar extent. Renal function is low compared to body size in neonates but rapidly matures within the first few months after birth. During adulthood there is a slow decline in renal function, about 1% per year, so that in the elderly a substantial degree of impairment is usually present.

The amount of drug entering the tubular lumen by filtration is dependent on the glomerular filtration rate and the extent of plasma binding of the drug; only unbound drug is filtered. In the proximal renal tubule, active, carriermediated tubular secretion also may add drug to the tubular fluid. Transporters such as P-glycoprotein and the multidrug resistance-associated protein-type 2 (MRP2) localized in the apical, brush-border membrane are largely responsible for the secretion of amphipathic anions and conjugated metabolites (such as glucuronides, sulfates, and glutathione adducts), respectively. Transport systems that are similar but more selective for organic cationic drugs (OCDs) are involved in the secretion of organic bases. Membrane transporters, mainly located in the distal renal tubule, also are responsible for any active reabsorption of drug from the tubular lumen back into the systemic circulation. However, most of such reabsorption occurs by nonionic diffusion.

In the proximal and distal tubules, the nonionized forms of weak acids and bases undergo net passive reabsorption. The concentration gradient for back-diffusion is created by the reabsorption of water with Na^+ and other inorganic ions. Since the tubular cells are less permeable to the ionized forms of weak electrolytes, passive reabsorption of these substances is pH-dependent. When the tubular urine is made more alkaline, weak acids are excreted more rapidly and to a greater extent, primarily because they are more ionized and passive reabsorption is decreased. When the tubular urine is made more acidic, the excretion of weak acids is reduced. Alkalinization and acidification of the urine have the opposite effects on the excretion of weak bases. In the treatment of drug poisoning, the excretion of some drugs can be hastened by appropriate alkalinization or acidification of the urine. Whether or not alteration of urine pH results in a signifi- cant change in drug elimination depends upon the extent and persistence of the pH change and the contribution of pH-dependent passive reabsorption to total drug elimination. The effect is greatest for weak acids and bases with p*Ka* values in the range of urinary pH (5 to 8). However, alkalinization of urine can produce a fourfold to sixfold increase in excretion of a relatively strong acid such as salicylate when urinary pH is changed from 6.4 to 8.0. The fraction of nonionized drug would decrease from 1% to 0.04%.

Biliary and Fecal Excretion

Transport systems analogous to those in the kidney also are present in the canalicular membrane of the hepatocyte, and these actively secrete drugs and metabolites into bile. P-glycoprotein transports a plethora of amphipathic, lipid-soluble drugs, whereas MRP2 is mainly involved in the secretion of conjugated metabolites of drugs (glutathione conjugates, glucuronides, and some sulfates). MRP2 also is involved in the excretion of endogenous compounds, and the Dubin-Johnson syndrome is caused by a genetically determined absence of this transporter. Active biliary secretion of organic cations also involves transporters. Ultimately, drugs and metabolites present in bile are released into the intestinal tract during the digestive process. Because secretory transporters such as P-glycoprotein also are expressed on the apical membrane of enterocytes, direct secretion of drugs and metabolites may occur from the systemic circulation into the intestinal lumen. Subsequently, drugs and metabolites can be reabsorbed back into the body from the intestine which, in the case of conjugated metabolites like glucuronides, may require their enzymatic hydrolysis by the intestinal microflora. Such enterohepatic recycling, if extensive, may prolong significantly the presence of a drug and its effects within the body prior to elimination by other pathways.

Excretion by Other Routes

Excretion of drugs into sweat, saliva, and tears is quantitatively unimportant. Elimination by these routes is dependent mainly upon diffusion of the nonionized, lipid-soluble form of drugs through the

epithelial cells of the glands and is pH-dependent. Drugs excreted in the saliva enter the mouth, where they are usually swallowed. The concentration of some drugs in saliva parallels that in plasma. Saliva therefore may be a useful biological fluid in which to determine drug concentrations when it is difficult or inconvenient to obtain blood. The same principles apply to excretion of drugs in breast milk. Since milk is more acidic than plasma, basic compounds may be slightly concentrated in this fluid, and the concentration of acidic compounds in the milk is lower than in plasma. Nonelectrolytes, such as ethanol and urea, readily enter breast milk and reach the same concentration as in plasma, independent of the pH of the milk. Although excretion into hair and skin also is quantitatively unimportant, sensitive methods of detection of drugs in these tissues have forensic significance.

METABOLISM OF DRUGS

The lipophilic characteristics of drugs that promote their passage through biological membranes and subsequent access to their site of action hinder their excretion from the body. Renal excretion of unchanged drug plays only a modest role in the overall elimination of most therapeutic agents, since lipophilic compounds filtered through the glomerulus are largely reabsorbed back into the systemic circulation during passage through the renal tubules. The metabolism of drugs and other xenobiotics into more hydrophilic metabolites is therefore essential for the elimination of these compounds from the body and termination of their biological activity. In general, biotransformation reactions generate more polar, inactive metabolites that are readily excreted from the body. However, in some cases, metabolites with potent biological activity or toxic properties are generated. Many of the metabolic biotransformation reactions leading to inactive metabolites of drugs also generate biologically active metabolites of endogenous compounds. The following discussion focuses on the biotransformation of drugs but is generally applicable to the metabolism of all xenobiotics as well as a number of endogenous compounds, including steroids, vitamins, and fatty acids.

Phase I and Phase II Metabolism

Drug biotransformation reactions are classified as either phase Ⅰ functionalization reactions or phase Ⅱ biosynthetic (conjugation) reactions. Phase Ⅰ reactions introduce or expose a functional group on the parent compound. Phase Ⅰ reactions generally result in the loss of pharmacological activity, although there are examples of retention or enhancement of activity. In rare instances, metabolism is associated with an altered pharmacological activity. Prodrugs are pharmacologically inactive compounds, designed to maximize the amount of the active species that reaches its site of action. Inactive prodrugs are converted rapidly to biologically active metabolites, often by the hydrolysis of an ester or amide linkage. If not rapidly excreted into the urine, the products of phase Ⅰ biotransformation reactions can then react with endogenous compounds to form a highly watersoluble conjugate.

Phase Ⅱ conjugation reactions lead to the formation of a covalent linkage between a functional group on the parent compound or phase Ⅰ metabolite with endogenously derived glucuronic acid, sulfate, glutathione, amino acids, or acetate. These highly polar conjugates are generally inactive and are excreted rapidly in the urine and feces. An example of an active conjugate is the 6-glucuronide metabolite of morphine, which is a more potent analgesic than its parent compound.

Site of Biotransformation

The metabolic conversion of drugs generally is enzymatic in nature. The enzyme systems involved in the biotransformation of drugs are localized in the liver, although every tissue examined has some metabolic activity. Other organs with significant metabolic capacity include the gastrointestinal tract, kidneys, and lungs. Following nonparenteral administration of a drug, a significant portion of the dose may be metabolically inactivated in either the intestinal epithelium or the liver before it reaches the systemic circulation. This first-pass metabolism significantly limits the oral availability of highly metabolized drugs. Within a given cell, most drugmetabolizing activity is found in the endoplasmic reticulum and the cytosol, although drug biotransformations also can occur in the mitochondria, nuclear envelope, and plasma membrane. Upon homogenization and differential centrifugation of tissues, the endoplasmic reticulum breaks up, and fragments of the membrane form microvesicles, referred to as microsomes. The drug-metabolizing enzymes in the endoplasmic reticulum therefore often are classified as