# GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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# CHAPTER 1

# PHARMACOKINETICS

## The Dynamics of Drug Absorption, Distribution, and Elimination

*Leslie Z. Benet, Deanna L. Kroetz, and Lewis B. Sheiner*

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 attained also depend upon the extent and rate of its absorption, distribution, binding or localization in tissues, biotransformation, and excretion. These factors are depicted in Figure 1–1.

## PHYSICOCHEMICAL FACTORS IN TRANSFER OF DRUGS ACROSS MEMBRANES

The absorption, distribution, biotransformation, and excretion of a drug all involve its passage across cell membranes. It is essential, therefore, to consider the mechanisms by which drugs cross membranes and the physicochemical properties of molecules and membranes that influence this transfer. Important characteristics of a drug are its molecular size and shape, solubility at the site of its absorption, degree of ionization, and relative lipid solubility of its ionized and nonionized forms.

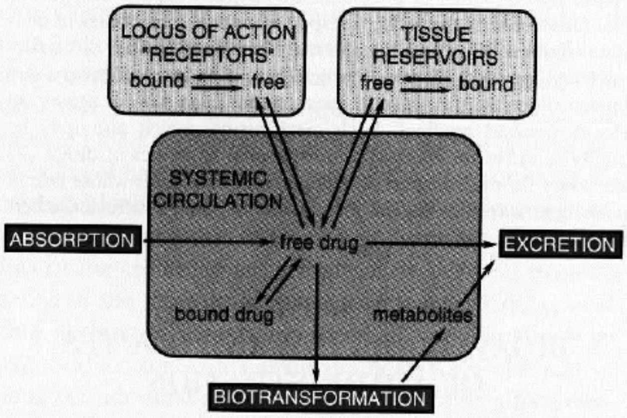


***Figure 1–1. Schematic representation of the interrelationship of the absorption, distribution, binding, biotransformation, and excretion of a drug and its concentration at its locus of action.***

Possible distribution and binding of metabolites are not depicted.

When a drug permeates a cell, it must obviously 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 these 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 oriented inward to form a continuous hydrophobic phase and their hydrophilic heads oriented outward. Individual lipid molecules in the bilayer 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 to elicit electrical or chemical signaling pathways and provide selective targets for drug actions.

**Passive Processes.** 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 and the lipid:water partition coefficient of the drug. 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 free 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. Most biological membranes are relatively permeable to water, either by diffusion or by flow that results from hydrostatic or osmotic differences across the membrane. Such bulk flow of water can carry with it small, water-soluble substances. Most cell membranes permit passage only of water, urea, and other small, water-soluble molecules by this mechanism. Such substances generally do not pass through cell membranes if their molecular masses are greater than 100 to 200 Da.

While most inorganic ions would seem to be sufficiently small to penetrate the membrane, their hydrated ionic radius is relatively large. The concentration gradient of many inorganic ions is largely determined by active transport (*e.g.*, $Na^+$ and $K^+$). The transmembrane potential frequently determines the distribution of other ions (*e.g.*, chloride) across the membrane. Channels with selectivity for individual ions are often controlled to allow regulation of specific ionic fluxes. Such mechanisms are of obvious importance in the generation of action potentials in nerve and muscle (*see* Chapter 6) and in transmembrane signaling events (*see* Chapter 2).

**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 $pK_a$ and the pH gradient across the membrane. To illustrate the effect of pH on distribution of drugs, the partitioning of a weak acid ($pK_a = 4.4$) between plasma (pH = 7.4) and gastric juice (pH = 1.4) is depicted in Figure 1–2. 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 easily 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 1–2. 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 $pK_a$ of 4.4 ($BH^+ \rightleftharpoons B + H^+$), the ratio would be reversed, as would the thick horizontal arrows in Figure 1–2, which indicate the predominant species at each pH. These considerations have obvious implications for the absorption and excretion of drugs, as will be 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.

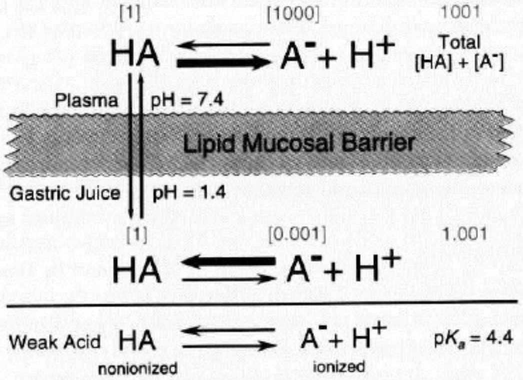


***Figure 1–2. Influence of pH on the distribution of a weak acid between plasma and gastric juice, separated by a lipid barrier.***

Bulk flow through intercellular pores is the major mechanism of passage of drugs across most capillary endothelial membranes, with the important exception of the central nervous system (CNS; *see* below). These intercellular gaps are sufficiently large that diffusion across most capillaries is limited by blood flow and not by the lipid solubility of drugs or pH gradients. This is an important factor in filtration across glomerular membranes in the kidney (*see* below). Tight junctions are characteristic of capillaries of the CNS and a variety of epithelia. Intercellular diffusion is consequently limited. Pinocytosis, the formation and movement of vesicles across cell membranes, has been implicated in drug absorption. However, the quantitative significance of pinocytosis probably is negligible.

**Carrier-Mediated Membrane Transport.** While passive diffusion through the bilayer is dominant in the absorption and distribution of most drugs, more active and selective mechanisms can play important roles. Active transport of some drugs occurs across neuronal membranes, the choroid plexus, renal tubular cells, and hepatocytes. The characteristics of active transport—selectivity, competitive inhibition by congeners, a requirement for energy, saturability, and movement against an electrochemical gradient—may be important in the mechanism of action of drugs that are subject to active transport or that interfere with the active transport of natural metabolites or neurotransmitters. The term *facilitated diffusion* describes a carrier-mediated transport process to which there is no input of energy, and movement of the substance in question thus cannot occur against an electrochemical gradient. Such mechanisms, which also may be highly selective for specific conformational structures of drugs, are necessary for the transport of endogenous compounds whose rate of movement across biological membranes by simple diffusion otherwise would be too slow.

## 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 extent to which a 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 that is absorbed from the stomach and intestine must first pass through the liver before it reaches the systemic circulation. If the drug is metabolized in the liver or excreted in the bile, some of the active 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 great, bioavailability will be substantially decreased (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. Moreover, factors that modify the absorption of a drug can change its bioavailability.

**Factors That Modify Absorption.** Many variables, in addition to the physicochemical factors that affect transport across membranes, influence the absorption of drugs. Absorption, regardless of the site, is dependent upon drug solubility. Drugs given in aqueous solution are more rapidly absorbed than those given in oily solution, suspension, or solid form, because they mix more readily with the aqueous phase at the absorptive site. For those given in solid form, the rate of dissolution may be the limiting factor in their absorption. Local conditions at the site of absorption alter solubility, particularly in the gastrointestinal tract. Aspirin, which is relatively insoluble in acidic gastric contents, is a common example of such a drug. The concentration of a drug influences its rate of absorption. Drugs introduced at an administration site in solutions of high concentration are absorbed more rapidly than are drugs in solutions of low concentration. The circulation to the site of absorption also affects drug absorption. Increased blood flow, brought about by massage or local application of heat, enhances the rate of drug absorption; decreased blood flow, produced by vasoconstrictor agents, shock, or other disease factors, can slow absorption. The area of the absorbing surface to which a drug is exposed is one of the more important determinants of the rate of drug absorption. Drugs are absorbed very rapidly from large surface areas such as the pulmonary alveolar epithelium, the intestinal mucosa, or, in a few cases after extensive application, the skin. The absorbing surface is determined largely by the route of administration. Each of these factors separately or in conjunction with one another may have profound effects on the clinical efficacy and toxicity of a drug.

**Enteral (Oral) vs. 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 1–1.

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 the incapability to absorb some drugs because of their physical characteristics (*e.g.,* polarity), 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 mucosa, the intestinal flora, 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 absorbed in active form. Availability is usually more rapid and more predictable than when a drug is given by mouth. The effective dose can therefore be more accurately selected. In emergency therapy, parenteral administration is particularly serviceable. If a patient is unconscious, uncooperative, or unable to retain anything given by mouth, parenteral therapy may be a necessity. The injection of drugs also has its disadvantages. Asepsis must be maintained, an intravascular injection may occur when it is not intended, pain may accompany the injection, and it is sometimes difficult for patients to perform the injections themselves if self-medication is necessary. Expense is another consideration.

**Oral Ingestion.** Absorption from the gastrointestinal tract is governed by factors that are generally applicable, such as surface area for absorption, blood flow to the site of absorption, the physical state of the drug, and its concentration at the site of absorption. 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. Thus, one might expect the absorption of weak acids to be optimal in the acidic environment of the stomach, whereas absorption of bases might be favored in the relatively alkaline small intestine. However, it is an oversimplification to extrapolate the pH-partition concept presented in Figure 1–2 to a comparison erent biological membranes, such as the ep

**Table 1–1**
**Some Characteristics of Common Routes of Drug Administration***

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

**See* text for more complete discussion and for other routes.

ithelia of the stomach and the intestine. The stomach is lined by a thick, mucus-covered membrane with a small surface area and high electrical resistance. The primary function of the stomach is digestive. In contrast, the epithelium of the intestine has an extremely large surface area; it is thin, it has low electrical resistance, and its primary function is to facilitate the absorption of nutrients. 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. The experimental data available from the classical work of Brodie (1964) and more recent studies all are consistent with the following conclusion: the nonionized form of a drug will be absorbed more rapidly than the ionized form at any particular site in the gastrointestinal tract. However, 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.

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-coated preparations 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 controlled-release, extendedrelease, 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 theoretical expectations. However, the clinician must be aware of some drawbacks of these products. 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 well-designed 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 first-pass metabolism by the liver. Hepatic first-pass metabolism is sufficient to prevent the appearance of any active nitroglycerin in the systemic circulation if the conventional tablet is swallowed.

**Rectal Administration.** The rectal route often is useful when oral ingestion is precluded by vomiting or when the patient is unconscious. 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 clearing 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.*** The factors concerned in absorption are circumvented by intravenous injection of drugs in aqueous solution, and the desired concentration of a drug in blood is obtained with an accuracy and immediacy not possible by any other procedure. In some instances, as in the induction of surgical anesthesia by a barbiturate, 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 assets 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. 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. Intravenous injection usually must be performed slowly and with constant monitoring of the responses of the patient.

***Subcutaneous.*** Injection of a drug into a subcutaneous site often is used. It can be used only for drugs that are not irritating to tissue; otherwise, severe pain, necrosis, and slough may occur. The rate of absorption following subcutaneous injection of a drug often is sufficiently constant and slow to provide a sustained effect. Moreover, it may be varied intentionally. For example, the rate of absorption of a suspension of insoluble insulin is slow compared with that of a soluble preparation of the hormone. The incorporation of a vasoconstrictor agent in a solution of a drug to be injected subcutaneously also retards absorption. Absorption of drugs implanted under the skin in a solid pellet form occurs slowly over a period of weeks or months; some hormones are effectively administered in this manner.

***Intramuscular.*** Drugs in aqueous solution are absorbed quite rapidly after intramuscular injection, depending upon the rate of blood flow to the injection site. Joggers who inject insulin into their thigh may experience a precipitous drop in blood sugar that is not seen following injection into the arm or abdominal wall, since running markedly increases blood flow to the leg. Generally, the rate of absorption following injection of an aqueous preparation into the deltoid or vastus lateralis is faster than when the injection is made into the gluteus maximus. The rate is particularly slower for females after injection into the gluteus maximus. This has been attributed to the different distribution of subcutaneous fat in males and females, since fat is relatively poorly perfused. Very obese or emaciated patients may exhibit unusual patterns of absorption following intramuscular or subcutaneous injection. Very slow, constant absorption from the intramuscular site results if the drug is injected in solution in oil or suspended in various other repository vehicles. Penicillin often is administered in this manner. Substances too irritating to be injected subcutaneously may sometimes be given intramuscularly.

***Intraarterial.*** Occasionally a drug is injected directly into an artery to localize its effect in a particular tissue or organ. However, this practice usually has dubious therapeutic value. Diagnostic agents are sometimes administered by this route. Intraarterial injection requires great care and should be reserved for experts. The first-pass and cleansing effects of the lung are not available when drugs are given by this route.

***Intrathecal.*** The blood–brain barrier and the blood–cerebrospinal fluid barrier often preclude or slow the entrance of drugs into the CNS. Therefore, when local and rapid effects of drugs on the meninges or cerebrospinal axis are desired, as in spinal anesthesia or acute CNS infections, drugs are sometimes injected directly into the spinal subarachnoid space.

***Intraperitoneal.*** The peritoneal cavity offers a large absorbing surface from which drugs enter the circulation rapidly, but primarily by way of the portal vein; first-pass hepatic losses are thus possible. Intraperitoneal injection is a common laboratory procedure, but it is seldom employed clinically. The dangers of producing infection and adhesions are too great to warrant the routine use of this route in human beings.

**Pulmonary Absorption.** Gaseous and volatile drugs may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the circulation is rapid by this route, because the surface area is large. The principles governing absorption and excretion of anesthetic and other therapeutic gases are discussed in Chapters 13, 14, and 16.

In addition, solutions of drugs can be atomized and the fine droplets in air (aerosol) inhaled. Advantages are the almost instantaneous absorption of a drug into the blood, avoidance of hepatic first-pass loss, and, in the case of pulmonary disease, local application of the drug at the desired site of action. For example, drugs can be given in this manner for the treatment of bronchial asthma (*see* Chapter 28). The main disadvantages are poor ability to regulate the dose, cumbersomeness of the methods of administration, and the fact that many gaseous and volatile drugs produce irritation of the pulmonary epithelium.

Pulmonary absorption is an important route of entry of certain drugs of abuse and of toxic environmental substances of varied composition and physical states (*see* Section XVII). Both local and systemic reactions to allergens may occur subsequent to inhalation.

**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 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 proportional to the surface area over which they are applied and to their lipid solubility, since the epidermis behaves as a lipid barrier (*see* Chapter 64). 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 (*e.g.*, 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. This method of administration is known as *inunction*. 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 recent innovations. 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 (*see* Chapter 65). 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 $\beta$-adrenergic antagonists are administered as ophthalmic drops. Local effects usually require absorption of the drug through the cornea; corneal infection or trauma may thus result in more rapid absorption. Ophthalmic delivery systems that provide prolonged duration of action (*e.g.*, 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.

**Bioequivalence.** Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be bioequivalent when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions. In the past, dosage forms of a drug from different manufacturers and even different lots of preparations from a single manufacturer sometimes differed in their bioavailability. Such differences were seen primarily among oral dosage forms of poorly soluble, slowly absorbed drugs. They result from differences in crystal form, particle size, or other physical characteristics of the drug that are not rigidly controlled in formulation and manufacture of the preparations. These factors affect disintegration of the dosage form and dissolution of the drug and hence the rate and extent of drug absorption.

The potential nonequivalence of different drug preparations has been a matter of concern. Strengthened regulatory requirements have resulted in few, if any, documented cases of nonequivalence between approved drug products. The significance of possible nonequivalence of drug preparations is further discussed in connection with drug nomenclature and the choice of drug name in writing prescription orders (*see* Appendix I).

## DISTRIBUTION OF DRUGS

After a drug is absorbed or injected into the bloodstream, it may be distributed into interstitial and cellular fluids. Patterns of drug distribution reflect certain physiological factors and physicochemical properties of drugs. An initial phase of distribution may be distinguished that reflects cardiac output and regional blood flow. Heart, liver, kidney, brain, and other well-perfused organs receive most of the drug during the first few minutes after absorption. Delivery of drug to muscle, most viscera, skin, and fat is slower, and these tissues may require several minutes to several hours before steady state is attained. A second phase of drug distribution may therefore be distinguished; this is also limited by blood flow, and it involves a far larger fraction of the body mass than does the first phase. Superimposed on patterns of distribution of blood flow are factors that determine the rate at which drugs diffuse into tissues. Diffusion into the interstitial compartment occurs rapidly because of the highly permeable nature of capillary endothelial membranes (except in the brain). Lipid-insoluble drugs that permeate membranes poorly are restricted in their distribution and hence in their potential sites of action. Distribution also may be limited by drug binding to plasma proteins, particularly albumin for acidic drugs and $\alpha_1$-acid glycoprotein for basic drugs. An agent that is extensively and strongly bound has limited access to cellular sites of action, and it may be metabolized and eliminated slowly. Drugs may accumulate in tissues in higher concentrations than would be expected from diffusion equilibria as a result of pH gradients, binding to intracellular constituents, or partitioning into lipid.

Drug that has accumulated in a given tissue may serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation. An example that illustrates many of these factors 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 thiopent [illegible] fuses 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 concentration of drug in the brain. A third phase of distribution for this drug is due to the slow, blood-flow–limited uptake by fat. With administration of successive doses of thiopental, accumulation of drug takes place in fat and other tissues that can store large amounts of the compound. These can become reservoirs for the maintenance of the plasma concentration, and therefore the brain concentration, at or above the threshold required for anesthesia. Thus, a drug that is short acting because of rapid redistribution to sites at which the agent has no pharmacological action can become long acting when these storage sites are "filled" and termination of the drug's action becomes dependent on biotransformation and excretion (*see* Bènet, 1978).

Since the difference in pH between intracellular and extracellular fluids is small (7.0 vs. 7.4), this factor can result in only a relatively small concentration gradient of drug across the plasma membrane. Weak bases are slightly concentrated inside of cells, while the concentration of weak acids is slightly lower in the cells than in extracellular fluids. Lowering the pH of extracellular fluid increases the intracellular concentration of weak acids and decreases that of weak bases, provided that the intracellular pH does not also change and that the pH change does not simultaneously affect the binding, biotransformation, or excretion of the drug. Elevating the pH produces the opposite effects (*see* Figure 1–2).

**Central Nervous System and Cerebrospinal Fluid.** The distribution of drugs to the CNS from the bloodstream is unique, mainly in that entry of drugs into the cerebrospinal fluid and extracellular space of the CNS is restricted. The restriction is similar to that across the gastrointestinal epithelium. Endothelial cells of the brain capillaries differ from their counterparts in most tissues by the absence of intercellular pores and pinocytotic vesicles. Tight junctions predominate, and aqueous bulk flow thus is severely restricted. This is not unique to the CNS capillaries (tight junctions appear in many muscle capillaries as well). It is likely that the unique arrangement of pericapillary glial cells also contributes to the slow diffusion of organic acids and bases into the CNS. The drug molecules probably must traverse not only endothelial but also perivascular cell membranes before reaching neurons or other target cells in the CNS. Cerebral blood flow is the only limitation to permeation of the CNS by highly lipid- [illegible] ugs. The rate of diffusion of drugs with increasing polarity into the CNS is proportional to the lipid solubility of the nonionized species.

Strongly ionized agents such as quaternary amines are normally unable to enter the CNS from the circulation. In addition, organic ions are extruded from the cerebrospinal fluid into blood at the choroid plexus by transport processes similar to those in the renal tubule. Lipid-soluble substances leave the brain by diffusion through the capillaries and the blood–choroid plexus boundary. Drugs and endogenous metabolites, regardless of lipid solubility and molecular size, also exit with bulk flow of the cerebrospinal fluid through the arachnoid villi.

The blood–brain barrier is adaptive in that exclusion of drugs and other foreign agents such as penicillin or tubocurarine protects the CNS against severely toxic effects. However, the barrier is neither absolute nor invariable. Very large doses of penicillin may produce seizures; meningeal or encephalic inflammation increases the local permeability. Maneuvers to increase permeability of the blood–brain barrier potentially are important to enhance the efficacy of chemotherapeutic agents that are used to treat infections or tumors localized in the brain.

**Drug Reservoirs.** As mentioned, the body compartments in which a drug accumulates are potential reservoirs for the drug. If stored drug is in equilibrium with that in plasma and is released as the plasma concentration declines, a concentration of the drug in plasma and at its locus of action is sustained, and pharmacological effects of the drug are prolonged. However, if the reservoir for the drug has a large capacity and fills rapidly, it so alters the distribution of the drug that larger quantities of the drug are required initially to provide a therapeutically effective concentration in the target organ.

***Plasma Proteins.*** Many drugs are bound to plasma proteins, mostly to plasma albumin for acidic drugs and to $\alpha_1$-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 equations are used to describe the free and bound concentrations (*see* Chapter 2). 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, statements that a given drug is bound to a specified extent apply only over a limited range of concentrations. The percentage values listed in Appendix II refer only to the therapeutic range of concentrations for each drug.

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. 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, plasma protein binding does *not* generally 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. If a drug is avidly transported or metabolized and its clearance, calculated on the basis of unbound drug, exceeds organ plasma flow, 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.

Since 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 been overemphasized. Since drug responses, both efficacious and toxic, are a function of unbound concentrations, steady-state unbound concentrations will only change when either drug input (dosing rate) or clearance of unbound drug is changed (*see* equation 1–1 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 from bound drug.

***Cellular Reservoirs.*** Many drugs accumulate in muscle and other cells in higher concentrations than in the extracellular fluids. If the intracellular concentration is high and if the binding is reversible, the tissue involved may represent a sizable drug reservoir, particularly if the tissue represents a large fraction of body mass. For example, during long-term administration of the antimalarial agent quinacrine, the concentration of the drug in liver may be several thousand times that in plasma. Accumulation in cells may be the result of active transport or, more commonly, binding. Tissue binding of drugs usually occurs to proteins, phospholipids, or nucleoproteins and is generally reversible.

***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-metal-ion 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.

***Transcellular Reservoirs.*** Drugs also cross epithelial cells and may accumulate in the transcellular fluids. The major transcellular reservoir is the gastrointestinal tract. Weak bases are passively concentrated in the stomach from the blood, because of the large pH differential between the two fluids, and some drugs are secreted in the bile in an active form or as a conjugate that can be hydrolyzed in the intestine. In these cases, and when an orally administered drug is slowly absorbed, the gastrointestinal tract serves as a drug reservoir.

Other transcellular fluids, including cerebrospinal fluid, aqueous humor, endolymph, and joint fluids, do not generally accumulate significant total amounts of drugs.

**Redistribution.** Termination of drug effect usually is by biotransformation and excretion, but it may also 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. The factors involved in redistribution of drugs have been discussed above.

**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. Drugs cross the placenta primarily by simple diffusion. Lipid-soluble, nonionized drugs readily enter the fetal blood from the maternal circulation. Penetration is least with drugs possessing a high degree of dissociation or low lipid solubility. The view that the placenta is a 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.

## BIOTRANSFORMATION OF DRUGS

The lipophilic characteristics of drugs that promote their passage through biological membranes and subsequent access to their site of action hinder their elimination 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 through the tubular membranes. The biotransformation of drugs and other xenobiotics into more hydrophilic metabolites is therefore essential for the termination of their biological activity, and the elimination of these compounds from the body. 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 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 Biotransformations.** Drug biotransformation reactions are classified as either phase I functionalization reactions or phase II biosynthetic 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 has been 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 water soluble conjugate.

Phase II conjugation reactions lead to the formation of a covalent linkage between a functional group on the parent compound with 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 glucuronide metabolite of morphine, which is a more potent analgesic [illegible]nt compound. High molecular weight conjugates excreted in the bile are subject to enzymatic cleavage of the conjugate bond by intestinal microflora and release of the parent drug back into the systemic circulation. This phenomenon of enterohepatic recirculation may be associated with a delayed elimination of drug from the body and a prolongation of effect.

**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 kidneys, gastrointestinal tract, skin, and lungs. Following nonparenteral administration of a drug, a significant portion of the dose may be metabolically inactivated in either the liver or intestines before it reaches the systemic circulation. This first-pass metabolism significantly limits the oral availability of highly metabolized drugs. Within a given cell, most drug-metabolizing 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 microsomal enzymes. The enzyme systems involved in phase I reactions are located primarily in the endoplasmic reticulum, while the phase II conjugation enzyme systems are mainly cytosolic. Often drugs biotransformed through a phase I reaction in the endoplasmic reticulum are conjugated in the cytosolic fraction of the same cell.

**Cytochrome P450 Monooxygenase System.** The cytochrome P450 enzyme family is the major catalyst of drug biotransformation reactions. Since its origin more than 3.5 billion years ago, the cytochrome P450 gene family has diversified to accommodate the metabolism of a growing number of environmental chemicals, food toxins, and drugs. The resulting superfamily of enzymes catalyzes a wide variety of oxidative and reductive reactions and has activity towards a chemically diverse group of substrates. Cytochrome P450 enzymes are heme-containing membrane proteins localized in the smooth endoplasmic reticulum of numerous tissues. These hemoproteins are in close association with a second membrane protein, NADPH–cytochrome P450 reductase, in a ratio of about ten cytochrome P450 molecules per one reductase. The flavoprotein reductase contains equimolar amounts of flavin mononucleotide and flavin adenine dinucleotide and is the source of one or both of the electrons required for the oxidation reaction. The interaction between the cytochrome P450 and reductase proteins is facilitated by the lipid bilayer in which they are embedded.

Oxidative reactions catalyzed by the microsomal monooxygenase system require the cytochrome P450 hemoprotein, NADPH–cytochrome P450 reductase, NADPH, and molecular oxygen. The multiple-step oxidation reaction is depicted schematically in Figure 1–3. The xenobiotic substrate reacts with the oxidized ($Fe^{3+}$) form of cytochrome P450 to form an enzyme–substrate complex. The cytochrome P450 reductase accepts an electron from NADPH, which in turn reduces the oxidized cytochrome P450–xenobiotic complex. The reduced ($Fe^{2+}$) cytochrome P450–substrate complex then reacts with molecular oxygen and a second electron from NADPH donated through the same flavoprotein reductase to form an activated oxygen species. In the final steps, one atom of oxygen is released as $H_2O$ and the second atom of oxygen is transferred to the substrate. Upon release of the oxidized substrate, the oxidized cytochrome P450 enzyme is regenerated. Oxidative biotransformations catalyzed by cytochrome P450 monooxygenases include aromatic and side chain hydroxylation, N-, O-, and S-dealkylation, N-oxidation, sulfoxidation, N-hydroxylation, deamination, dehalogenation, and desulfuration. A number of reductive reactions also are catalyzed by cytochrome P450 enzymes, generally under conditions of low oxygen tension. The only common structural feature of the diverse group of xenobiotics oxidized by cytochrome P450 enzymes is their high lipid solubility. Details and examples of cytochrome P450–catalyzed biotransformations are shown in Table 1–2.

Twelve cytochrome P450 gene families have been identified in human beings, and a number of distinct cytochrome P450 enzymes often exist within a single cell. A standard classification system for the cytochrome P450 multigene family is based on the sequence similarity of the individual proteins. Members of a given gene family have >40% amino acid identity. A given cytochrome P450 family is further divided into subfamilies, such that protein sequences within the same subfamily are >55% identical. The cytochrome P450 1, 2,

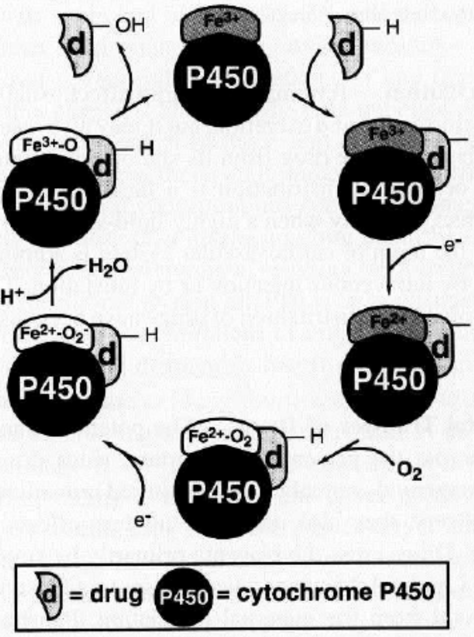
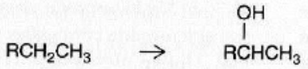
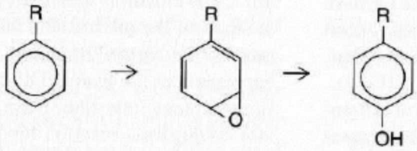
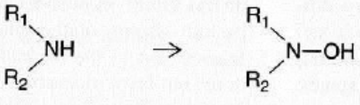
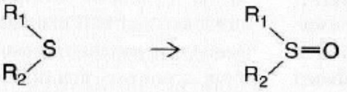
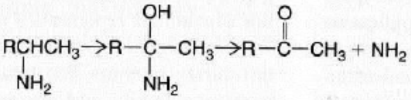
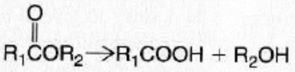
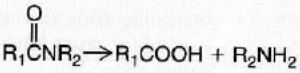
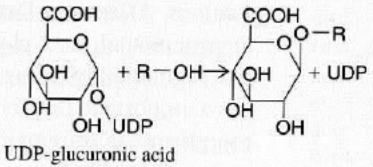
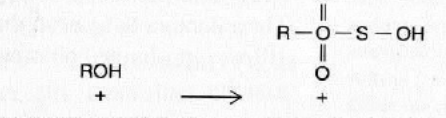
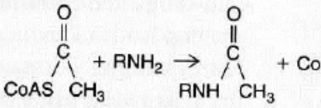


*Figure 1–3. Cytochrome P450 mechanism of oxygen activation and drug oxidation.*

The heme iron at the active site is shown as Fe. The electrons are supplied from NADPH via cytochrome P450 reductase.

**Table 1–2**
**Major Drug Biotransformation Reactions**

| | *Reaction* | *Examples* |
|---|---|---|
| I. OXIDATIVE REACTIONS | | |
| N-Dealkylation | $\mathrm{RNHCH_3 \rightarrow RNH_2 + CH_2O}$ | Imipramine, diazepam, codeine, erythromycin, morphine, tamoxifen, theophylline |
| O-Dealkylation | $\mathrm{ROCH_3 \rightarrow ROH + CH_2O}$ | Codeine, indomethacin, dextromethorphan |
| Aliphatic hydroxylation |  $\mathrm{RCH_2CH_3 \rightarrow R\overset{\overset{OH}{\vert}}{C}HCH_3}$ | Tolbutamide, ibuprofen, pentobarbital, meprobamate, cyclosporine, midazolam |
| Aromatic hydroxylation |  | Phenytoin, phenobarbital, propanolol, phenylbutazone, ethinyl estradiol |
| N-Oxidation | $\mathrm{RNH_2 \rightarrow RNHOH}$ | Chlorpheniramine, dapsone |
| |  | Guanethidine, quinidine, acetaminophen |
| S-Oxidation |  | Cimetidine, chlorpromazine, thioridazine |
| Deamination |  $\mathrm{R\underset{\underset{NH_2}{\vert}}{C}HCH_3 \rightarrow R-\overset{\overset{OH}{\vert}}{\underset{\underset{NH_2}{\vert}}{C}}-CH_3 \rightarrow R-\overset{\overset{O}{\Vert}}{C}-CH_3 + NH_2}$ | Diazepam, amphetamine |
| II. HYDROLYSIS REACTIONS | | |
| |  $\mathrm{R_1\overset{\overset{O}{\Vert}}{C}OR_2 \rightarrow R_1COOH + R_2OH}$ | Procaine, aspirin, clofibrate |
| |  $\mathrm{R_1\overset{\overset{O}{\Vert}}{C}NR_2 \rightarrow R_1COOH + R_2NH_2}$ | Lidocaine, procainamide, indomethacin |
| III. CONJUGATION REACTIONS | | |
| Glucuronidation |  UDP-glucuronic acid | Acetaminophen, morphine, diazepam |
| Sulfation |  3′-phosphoadenosine-5′-phosphosulfate (PAPS) → 3′-phosphoadenosine-5′-phosphate | Acetaminophen, steroids, methyldopa |
| Acetylation |  acetyl-coenzyme A | Sulfonamides, isoniazid, dapsone, clonazepan |

and 3 families (*CYP1*, *CYP2*, and *CYP3*) encode the enzymes involved in the majority of all drug biotransformations, while the gene products of the remaining cytochrome P450 families are important in the metabolism of endogenous compounds such as steroids and fatty acids. The relative contribution of the major human cytochrome P450 enzymes in the metabolism of drugs is illustrated in Figure 1–4. As a result of the relatively low substrate specificity among the cytochrome P450 proteins, two or more individual enzymes often can catalyze a given biotransformation reaction. CYP3A4 is involved in the biotransformation of a majority of all drugs and is expressed at significant levels extrahepatically. It is now recognized that extensive metabolism by CYP3A4 in the gastrointestinal tract is a significant factor contributing to the poor oral bioavailability of many drugs.

**Hydrolytic Enzymes.** The reactions of the major hydrolytic enzymes are illustrated in Table 1–2. A number of nonspecific esterases and amidases have been identified in the endoplasmic reticulum of human liver, intestine, and other tissues. The alcohol and amine groups exposed following hydrolysis of esters and amides are suitable substrates for conjugation reactions. Microsomal epoxide hydrolase is found in the endoplasmic reticulum of essentially all tissues and is in close proximity to the cytochrome P450 enzymes. Epoxide hydrolase generally is considered a detoxification enzyme, hydrolyzing highly reactive arene oxides generated from cytochrome P450 oxidation reactions to inactive, water-soluble transdihydrodiol metabolites. Protease and peptidase enzymes are widely distributed in many tissues and are involved in the biotransformation of polypeptide drugs. With the increased interest in the therapeutic application of proteins and peptides, these enzymatic reactions have assumed greater importance. Delivery of such drugs across biological membranes requires the inhibition of these enzymes or the masking of their substrates.

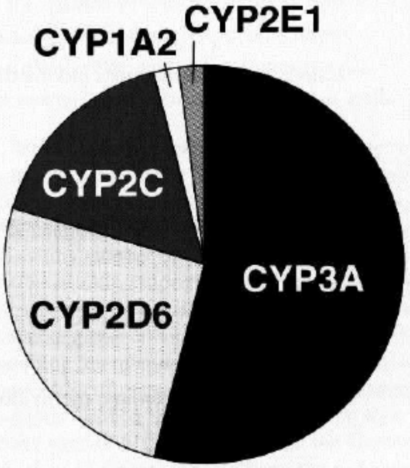


***Figure 1–4. The proportion of drugs metabolized by the major cytochrome P450 enzymes.***

Estimates are based on a compilation of literature reports. In many cases, a single drug is included in more than one category. The value for CYP2C metabolism reflects metabolism by CYP2C9, CYP2C10, CYP2C18, and CYP2C19.

**Conjugation Reactions.** The hallmark of phase II conjugation reactions is their requirement for energy. Glucuronidation is quantitatively the most important conjugation reaction. Uridine diphosphate glucuronosyltransferases (UDP-glucuronosyltransferases) catalyze the transfer of an activated glucuronic acid molecule to aromatic and aliphatic alcohols, carboxylic acids, amines, and free sulfhydryl groups of both exogenous and endogenous compounds, to form O-, N-, and S-glucuronide conjugates. The increased water solubility of the glucuronide conjugates promotes their elimination in the urine or bile. Unlike most phase II reactions, which are cytosolic in nature, the UDP-glucuronosyltransferases are microsomal enzymes. Their location in the microsomal membrane facilitates direct access to the metabolites formed in phase I reactions. In addition to high levels of expression in the liver, UDP-glucuronosyltransferases are also found in the kidney, intestine, brain, and skin. Sulfation also is an important conjugation reaction for hydroxyl groups. Cytosolic sulfotransferases catalyze the transfer of inorganic sulfur from the activated 3′-phosphoadenosine-5′-phosphosulfate donor molecule to the hydroxyl group on phenols and aliphatic alcohols. The relative capacity and affinity of the glucuronosyltransferases and the sulfotransferases lead to the formation of phenolic sulfate conjugates at low doses but favor glucuronide conjugates at high doses. A family of N-acetyltransferases is responsible for the acetylation of amines, hydrazines, and sulfonamides. In contrast to most drug conjugates, acetylated metabolites often are less water soluble than the parent drug, a property that prolongs their elimination from the body. Conjugation of electrophilic metabolites of xenobiotics with the tripeptide glutathione represents a major detoxification pathway for drugs and carcinogens (*see* Commandeur *et al.,* 1995). The glutathione S-transferase enzymes that catalyze these reactions are members of a multigene family and are expressed in virtually all tissues. Glutathione conjugates are cleaved to cysteine derivatives and subsequently are acetylated by a series of enzymes located primarily in the kidney to give N-acetylcysteine conjugates, collectively referred to as mercapturic acids. Mercapturic acid derivates are the ultimate metabolites excreted in the urine. Methylation and conjugation with the amino acids glycine, glutamine, and taurine are less common reactions for drugs but represent important reactions for endogenous compounds.

**Factors Affecting Drug Biotransformation.** Genetic, environmental, and physiological factors are involved in the regulation of drug biotransformation reactions. The most important factors are genetically determined polymorphisms in drug oxidations and conjugations, concomitant use of other drugs, exposure to environmental pollutants and industrial chemicals, disease, state, and age. These factors have been thought responsible for decreased efficacy, prolonged pharmacological effects, and increased toxicity.

***Induction.*** An increased synthesis of *de novo* cytochrome P450 protein is associated with exposure to certain drugs and environmental pollutants. This enzyme induction leads to an increased rate of biotransformation and corresponding decreases in the availability of the parent drug. For drugs that are metabolized to reactive species, induction may be associated with increased toxicity. In some cases, a given compound can induce both the biotransformation of other compounds and its own metabolism. A well-characterized example of this so-called autoinduction occurs with the anticonvulsant carbamazepine.

Inducers generally are specific for a given cytochrome P450 family, although within a family structurally diverse chemicals may have similar effects. For example, exposure to polycyclic aromatic hydrocarbons from industrial pollutants, cigarette smoke, and charbroiled meats results in dramatic induction of the CYP1A family both in the liver and extrahepatically. Prototype inducers of other cytochrome P450 enzymes include glucocorticoids and anticonvulsants for CYP3A4, and isoniazid, acetone, and chronic ethanol consumption for CYP2E1. Many inducers of cytochrome P450s also induce enzymes involved in phase II biotransformations, such as glucuronosyltransferases and glutathione transferases.

***Inhibition.*** Inhibition of drug biotransformation enzymes results in elevated levels of the parent drug, prolonged pharmacological effects, and an increased incidence of drug-induced toxicity. Competition between two or more drugs for the active site of the same enzyme may lead to a decrease in the metabolism of one of these agents, depending on the relative concentrations of each substrate and their affinities for the enzyme. Inhibition of *CYP2D6* by quinidine is a clinically significant example of competitive inhibition. Cimetidine and ketoconazole inhibit oxidative drug metabolism by forming a tight complex with the heme iron of cytochrome P450. In the case of macrolide antibiotics such as erythromycin and troleandomycin, a metabolite of these compounds is the heme-binding species. Suicide inactivators of cytochrome P450 enzymes result in the destruction of heme. Secobarbital and synthetic steroids, such as norethindrone and ethinyl estradiol, are examples of suicide inactivators. A common mechanism of inhibition for some of the phase II enzymes is the depletion of necessary cofactors.

***Genetic Polymorphisms.*** Genetic differences in the ability of individuals to metabolize a drug through a given pathway are recognized as an important contributor to the large interindividual differences in biotransformation within a population. Phenotypic differences in the amount of drug excreted through a polymorphically controlled pathway lead to the classification of individuals as extensive (rapid) or poor (slow) metabolizers. In many cases, impaired metabolism of a drug through a polymorphic pathway has been associated with an increased incidence of adverse effects in the slow metabolizer population. All major deficiencies in drug-metabolizing activity are inherited as autosomally recessive traits.

The first such genetic polymorphism associated with drug biotransformation was described over 30 years ago for the N-acetylation of isoniazid. Other drugs with significant metabolism through a polymorphic N-acetylation pathway are procainamide, hydralazine, dapsone, and caffeine. Biochemical and molecular evidence now support decreased levels of functional protein in the livers of slow acetylators as a result of translational changes. The incidence of the slow acetylator phenotype is around 50% in American whites and blacks, 60% to 70% in Northern Europeans, and only 5% to 10% in persons of Asian descent. An association between the slow acetylator phenotype and the incidence of bladder cancer and another between the rapid acetylator phenotype and the incidence of colorectal cancer have been suggested from initial epidemiological studies.

The most common genetic polymorphisms associated with oxidative drug metabolism are the debrisoquine and mephenytoin polymorphisms. A deficiency in debrisoquine hydroxylase activity in a subset of the population reflects one or more mutations in the *CYP2D6* gene, which lead to CYP2D6 proteins that are either truncated or have altered enzyme activity. Individuals may be phenotyped for their CYP2D6 metabolism status by administration of a single dose of debrisoquine and measurement of the urinary ratio of unchanged drug to 4-hydroxydebrisoquine. Large-scale CYP2D6 phenotyping studies indicate a 5% to 10% incidence of the slow metabolizer phenotype in whites and about a 1% incidence in Asians. In 95% of the population, the CYP2D6 phenotype can now be correctly predicted from a single blood sample using genotyping procedures. A growing number of cardiovascular agents, psychoactive agents, and morphine derivatives are now recognized as CYP2D6 substrates. Impaired metabolism of encainide, flecainide, metoprolol, and perphenazine in slow metabolizers of debrisoquine is associated with an increased incidence of adverse effects. Associations between an extensive metabolizer CYP2D6 phenotype and the incidence of lung and bladder cancers remain controversial. A genetic polymorphism also has been described for the stereoselective hydroxylation of S-mephenytoin at the 4′-position. Poor metabolizers of S-mephenytoin 4′-hydroxylation constitute 3% to 5% of the white population and 20% of Asians. Omeprazole and other proton pump inhibitors are substrates for this cytochrome P450 enzyme. The major defect responsible for the S-mephenytoin poor metabolizer phenotype is a single base pair mutation in *CYP2C19*, which creates an aberrant splice site and introduces a premature stop codon, leading to the translation of a truncated and inactive CYP2C19 protein.

***Disease.*** Impairment of normal liver function in patients with hepatitis, alcoholic liver disease, fatty liver disease, biliary cirrhosis, and hepatocarcinomas potentially can lead to alterations in hepatic drug biotransformation. The degree to which cytochrome P450 monooxygenase activity and hepatic elimination are decreased will be a function of the severity of the liver damage. A decreased hepatic biotransformation of tolbutamide, diazepam, and morphine in patients with hepatic dysfunction has been associated with exaggerated pharmacological responses. Decreases in hepatic blood flow resulting from cardiac insufficiency or $\beta$-adrenergic blockade also can affect the rate of hepatic biotransformation. The metabolism of drugs with a high hepatic extraction ratio is limited by liver blood flow. For such drugs, a decreased hepatic blood flow would result in a decrease in the rate of biotransformation and clearance of the parent drug, and therefore a prolonged effect. Examples of high extraction ratio drugs whose elimination likely is to be altered by changes in liver blood flow include lidocaine, propranolol, verapamil, and amitriptyline.

***Age and Gender.*** Functional cytochrome P450 enzymes can be detected relatively early in fetal development, although the oxidative metabolism rates are lower than those found postnatally. The significance of individual cytochrome P450 enzymes in fetal biotransformation reactions has not been characterized. However, a role for the CYP3A family in fetal biotransformations is supported by the presence of a unique cytochrome P450, CYP3A7, which is expressed exclusively in the fetus. Glucuronidation, sulfation, glutathione conjugation, and epoxide hydrolysis also are active at low levels in the fetus. Newborns are able to catalyze efficiently most phase I biotransformation reactions, although the rate of these reactions is generally slower than that in adults. A marked impairment of bilirubin glucuronidation at birth contributes to hyperbilirubinemia in newborns. Both phase I and phase II enzyme systems begin to mature gradually following the first 2 weeks of life, although the pattern of development is variable for the different enzymes.

In general, age-related decreases in liver mass, hepatic enzyme activity, and hepatic blood flow result in a decrease in the overall metabolic capacity of the liver in the elderly. Decreases in the hepatic biotransformation of high hepatic extraction ratio drugs in the elderly are predicted from the decrease in liver blood flow, although the large degree of interindividual variability in age- and disease-related changes in organ function makes it difficult to make generalizations. It is noteworthy, however, that age-related decreases in hepatic biotransformation are principally associated with the cytochrome P450 monooxygenase system, while alternate metabolic pathways do not appear to be markedly affected by age. Clinical reports of decreased oxidation of estrogens and benzodiazepines in females relative to males suggest that gender-dependent variations in drug biotransformations also may be important in the pharmacological and toxic response of certain drugs. At this time, generalizations about such gender-specific differences in drug metabolism are premature.

**Metabolic Drug Interactions.** The coadministration of two or more drugs often is associated with a change in the clearance of one of the agents. Although drug interactions can lead to changes in absorption, protein binding, and urinary excretion, the effect on biotransformation generally is more pronounced. Metabolism-based drug interactions are associated largely with phase I metabolism through the cytochrome P450 enzyme system. Drugs that are metabolized by the same enzyme will competitively interact with each other for a binding site on the enzyme, thereby decreasing the rate of metabolism of the lower affinity drug. If the affected pathway represents the major route of elimination for the drug, then increased plasma levels of parent drug and prolonged or exaggerated pharmacological effects are possible. In many cases, competitive inhibition of metabolism through one pathway is masked by a compensatory increase in biotransformation through alternate pathways. Macrolide antibiotics and azole antifungals inhibit the elimination of a number of drugs by competition for CYP3A4. Inhibition of the CYP3A4-mediated metabolism of warfarin, carbamazepine, cyclosporine, and midazolam by erythromycin have been associated with toxic levels of parent drug. The inhibition of phenytoin biotransformation by dicumarol often is associated with ataxia and drowsiness. As we increase our understanding of the individual cytochrome P450 enzymes responsible for specific metabolic pathways, it will be possible to assess the probability of adverse effects resulting from multiple-drug therapy. Clinically significant drug interactions also have been associated with other phase I enzymes, including epoxide hydrolase and xanthine oxidase. Coadministration of the anticonvulsants valproic acid and carbamazepine results in increased plasma levels of a pharmacologically active metabolite of carbamazepine, carbamazepine-10,11-epoxide, in parallel with signs of neurotoxicity. The carbamazepine–valproic acid interaction is explained by the potent inhibitory effect of valproic acid on microsomal epoxide hydrolase, which results in a decreased clearance of carbamazepine-10,11-epoxide.

Drug–drug interactions also can occur when one drug induces the metabolism of a second drug. In this case, the clearance of the drug will be increased and the pharmacological effect diminished. The barbiturates are recognized as inducers of the metabolism of a number of drugs, including chlorpromazine, doxorubicin, estradiol, and phenytoin. Rifampin is a potent inducer of both gut and hepatic CYP3A4, and leads to significant increases in the clearance of corticosteroids, cyclosporine, oral contraceptives, quinidine, diazepam, warfarin, and digoxin. In many cases, the dosage of the affected drug must be increased during rifampin therapy in order to maintain therapeutic effects. Similarly, women are advised to use an alternative to oral contraceptives for birth control during rifampin therapy.

## EXCRETION OF DRUGS

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

The kidney is the most important organ for elimination of drugs and their metabolites. Substances excreted in the feces are mainly unabsorbed orally ingested drugs or metabolites excreted in the bile and not reabsorbed from the intestinal tract. 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 (*see* Chapters 13, 14, and 16); 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.

The amount of drug entering the tubular lumen by filtration is dependent on its fractional plasma protein binding and glomerular filtration rate. In the proximal renal tubule, certain organic anions and cations are added to the glomerular filtrate by active, carrier-mediated tubular secretion. Many organic acids (such as penicillin) and metabolites (such as glucuronides) are transported by the system that secretes naturally occurring substances such as uric acid; organic bases, such as tetraethylammonium, are transported by a separate system that secretes choline, histamine, and other endogenous bases. The carrier systems are relatively nonselective, and organic ions of similar charge compete for transport. Both transport systems also can be bidirectional, and at least some drugs are both secreted and actively reabsorbed. However, transport of most exogenous ions is predominantly secretory. The outstanding example of the bidirectional tubular transport of an endogenous organic acid is uric acid.

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, 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 alteration of urine pH results in a significant 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 $pK_a$ 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.** Many metabolites of drugs formed in the liver are excreted into the intestinal tract in the bile. These metabolites may be excreted in the feces; more commonly, they are reabsorbed into the blood and ultimately excreted in the urine. Both organic anions, including glucuronides, and organic cations are actively transported into bile by carrier systems similar to those that transport these substances across the renal tubule. Both transport systems are nonselective, and ions of like charge may compete for transport. Steroids and related substances are transported into bile by a third carrier system. The effectiveness of the liver as an excretory organ for glucuronide conjugates is very much limited by their enzymatic hydrolysis after the bile is mixed with the contents of the small intestine, and the parent drug can be reabsorbed from the intestine. Thus, such compounds may undergo extensive biliary cycling with eventual excretion by the kidney.

**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 may therefore 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 toxic metals in these tissues have forensic significance. Arsenic in Napoleon's hair, detected 150 years after administration, has raised interesting questions about how he died, and by whose hand. Mozart's manic behavior during the preparation of his last major work, the *Requiem,* may have been due to mercury poisoning; traces of the metal have been found in his hair.

## CLINICAL PHARMACOKINETICS

A fundamental hypothesis of clinical pharmacokinetics is that a relationship exists between the pharmacological or toxic response to a drug and the accessible concentration of the drug (*e.g.,* in blood). This hypothesis has been documented for many drugs (*see* Appendix II), although it is apparent for some drugs that no clear or simple relationship has been found between pharmacological effect and concentration in plasma. In most cases, as depicted in Figure 1–1, the concentration of drug in the systemic circulation will be related to the concentration of drug at its sites of action. The pharmacological effect that results may be the clinical effect desired, a toxic effect, or, in some cases, an effect unrelated to efficacy or toxicity. Clinical pharmacokinetics attempts to provide both a more quantitative relationship between dose and effect and the framework with which to interpret measurements of concentrations of drugs in biological fluids. The importance of pharmacokinetics in patient care rests on the improvement in efficacy that can be attained by attention to its principles when dosage regimens are chosen and modified.

The various physiological and pathophysiological variables that dictate adjustment of dosage in individual patients often do so as a result of modification of pharmacokinetic parameters. The three most important parameters are *clearance,* a measure of the body's ability to eliminate drug; *volume of distribution,* a measure of the apparent space in the body available to contain the drug; and *bioavailability,* the fraction of drug absorbed as such into the systemic circulation. Of lesser importance are the *rates* of availability and distribution of the agent.

## Clearance

Clearance is the most important concept to be considered when a rational regimen for long-term drug administration is to be designed. The clinician usually wants to maintain steady-state concentrations of a drug within a known therapeutic range (*see* Appendix II). Assuming complete bioavailability, the steady state will be achieved when the rate of drug elimination equals the rate of drug administration:

$$\text{Dosing rate} = CL \cdot C_{ss} \tag{1–1}$$

where $CL$ is clearance and $C_{ss}$ is the steady-state concentration of drug. Thus, if the desired steady-state concentration of drug in plasma or blood is known, the rate of clearance of drug by the patient will dictate the rate at which the drug should be administered.

The concept of clearance is extremely useful in clinical pharmacokinetics because clearance of a given drug usually is constant over the range of concentrations encountered clinically. This is true because systems for elimination of drugs usually are not saturated and, thus, the *absolute* rate of elimination of the drug is essentially a linear function of its concentration in plasma. A synonymous statement is that the elimination of most drugs follows first-order kinetics—a constant *fraction* of drug is eliminated per unit of time. If mechanisms for elimination of a given drug become saturated, the kinetics become zero-order—a constant *amount* of drug is eliminated per unit of time. Under such a circumstance, clearance becomes variable. Principles of drug clearance are similar to those of renal physiology, where, for example, creatinine clearance is defined as the rate of elimination of creatinine in the urine relative to its concentration in plasma. At the simplest level, clearance of a drug is the rate of elimination by all routes normalized to the concentration of drug $C$ in some biological fluid:

$$CL = \text{Rate of elimination}/C \tag{1–2}$$

It is important to note that clearance does not indicate how much drug is being removed but, rather, the volume of biological fluid such as blood or plasma that would have to be completely freed of drug to account for the elimination. Clearance is expressed as a volume per unit of time. Clearance usually is further defined as blood clearance ($CL_b$), plasma clearance ($CL_p$), or clearance based on the concentration of unbound or free drug ($CL_u$), depending on the concentration measured ($C_b$, $C_p$, or $C_u$).

Clearance by means of various organs of elimination is additive. Elimination of drug may occur as a result of processes that occur in the kidney, liver, and other organs. Division of the rate of elimination by each organ by a concentration of drug (*e.g.,* plasma concentration) will yield the respective clearance by that organ. Added together, these separate clearances will equal total systemic clearance:

$$CL_{renal} + CL_{hepatic} + CL_{other} = CL_{systemic} \tag{1–3}$$

Other routes of elimination could include that in saliva or sweat, partition into the gut, and metabolism at other sites.

Total systemic clearance may be determined at steady state by using equation 1–1. For a single dose of a drug with complete bioavailability and first-order kinetics of elimination, total systemic clearance may be determined from mass balance and the integration of equation 1–2 over time.

$$CL = \text{Dose}/AUC \tag{1–4}$$

where $AUC$ is the total area under the curve that describes the concentration of drug in the systemic circulation as a function of time (from zero to infinity).

***Examples.*** In Appendix II, the plasma clearance for cephalexin is reported as 4.3 ml $\cdot$ min$^{-1}$ $\cdot$ kg$^{-1}$, with 91% of the drug excreted unchanged in the urine. For a 70-kg man, the total body clearance from plasma would be 300 ml/min, with renal clearance accounting for 91% of this elimination. In other words, the kidney is able to excrete cephalexin at a rate such that approximately 273 ml of plasma would be freed of drug per minute. Because clearance usually is assumed to remain constant in a stable patient, the total rate of elimination of cephalexin will depend on the concentration of drug in the plasma (equation 1–2). Propranolol is cleared at a rate of 12 ml $\cdot$ min$^{-1}$ $\cdot$ kg$^{-1}$ (or 840 ml/min in a 70-kg man), almost exclusively by the liver. Thus, the liver is able to remove the amount of drug contained in 840 ml of plasma per minute. Of the drugs listed in Appendix II, one of the highest values of plasma clearance is that for labetalol—1750 ml/min; this value exceeds the rate of plasma (and blood) flow to the liver, the dominant organ for elimination of this drug. However, because labetalol partitions readily into red blood cells ($C_{rbc}/C_p = 1.8$), the amount of drug delivered to the excretory organ is considerably higher than suspected from measurement of its concentration in plasma. The relationship between plasma and blood clearance at steady state is given by:

$$\frac{CL_p}{CL_b} = \frac{C_b}{C_p} = 1 + H\left(\frac{C_{rbc}}{C_p} - 1\right) \tag{1–5}$$

One may solve for labetalol clearance from blood by substituting the red blood cell to plasma concentration ratio and the average value for the hematocrit ($H = 0.45$). Clearance of labetalol, when measured in terms of its concentration in blood, is actually 1290 ml/min, a more reasonable value. Thus, the plasma clearance may assume values that are not "physiological." A drug with an extremely low concentration in plasma that is concentrated in erythrocytes (*e.g.,* mecamylamine) can show a plasma clearance of tens of liters per minute. However, if the concentration in blood is used to define clearance, the maximal clearance possible is equal to the sum of blood flows to the various organs of elimination.

As mentioned, clearance of most drugs is constant over the range of concentration in plasma or blood that is encountered in clinical settings. This means that elimination is not saturated and the rate of elimination of drug is directly proportional to its concentration (equation 1–2). For drugs that exhibit saturable or dose-dependent elimination, clearance will vary with the concentration of drug, often according to the following equation:

$$\text{Total plasma clearance} = v_m/(K_m + C_p) \tag{1–6}$$

where $K_m$ represents the plasma concentration at which half of the maximal rate of elimination is reached (in units of mass/volume) and $v_m$ is equal to the maximal rate of elimination (in units of mass/time). This equation is entirely analogous to the Michaelis–Menten equation for enzyme kinetics. Design of dosage regimens for such drugs is more complex (*see* below).

A further definition of clearance is useful for understanding the effects of pathological and physiological variables on drug elimination, particularly with respect to an individual organ. The rate of elimination of a drug by an individual organ can be defined in terms of the blood flow to the organ and the concentration of drug in the blood. The rate of presentation of drug to the organ is the product of blood flow ($Q$) and the arterial drug concentration ($C_A$), and the rate of exit of drug from the organ is the product of blood flow and the venous drug concentration ($C_V$). The difference between these rates at steady state is the rate of drug elimination:

$$\begin{aligned}\text{Rate of elimination} &= Q \cdot C_A - Q \cdot C_V \\ &= Q(C_A - C_V)\end{aligned} \tag{1–7}$$

Division of equation 1–7 by the concentration of drug that enters the organ of elimination, $C_A$, yields an expression for clearance of the drug by the organ in question:

$$CL_{organ} = Q\left(\frac{C_A - C_V}{C_A}\right) = Q \cdot E \tag{1–8}$$

The expression $(C_A - C_V)/C_A$ in equation 1–8 can be referred to as the extraction ratio for the drug ($E$).

**Hepatic Clearance.** The concepts developed in equation 1–8 have important implications for drugs that are eliminated by the liver. Consider a drug that is efficiently removed from the blood by hepatic processes—biotransformation and/or excretion of unchanged drug into the bile. In this instance, the concentration of drug in the blood leaving the liver will be low, the extraction ratio will approach unity, and the clearance of the drug from blood will become limited by hepatic blood flow. Drugs that are cleared efficiently by the liver (*e.g.,* drugs in Appendix II with clearances greater than 6 ml · min$^{-1}$ · kg$^{-1}$, such as chlorpromazine, diltiazem, imipramine, lidocaine, morphine, and propranolol) are restricted in their rate of elimination, not by intrahepatic processes, but by the rate at which they can be transported in the blood to hepatic sites of elimination.

Additional complexities also have been considered. For example, the equations presented above do not account for drug binding to components of blood and tissues, nor do they permit an estimation of the intrinsic ability of the liver or kidney to eliminate a drug in the absence of limitations imposed by blood flow. Extensions of the relationships of equation 1–8 to include expressions for protein binding and intrinsic clearance have been proposed for a number of models of hepatic elimination (*see* Roberts *et al.,* 1988). All of these models indicate that, when the capacity of the eliminating organ to metabolize the drug is large in comparison with the rate of presentation of drug, the clearance will approximate the organ blood flow. In contrast, when the metabolic capability is small in comparison to the rate of drug presentation, the clearance will be proportional to the unbound fraction of drug in blood and the intrinsic clearance. Appreciation of these concepts allows one to understand a number of possibly puzzling experimental results. For example, enzyme induction or hepatic disease may change the rate of drug metabolism in an isolated hepatic microsomal enzyme system but not change clearance in the whole animal. For a drug with a high extraction ratio, clearance is limited by blood flow, and changes in the intrinsic clearance due to enzyme induction or hepatic disease should have little effect. Similarly, for drugs with high extraction ratios, changes in protein binding due to disease or competitive binding interactions should have little effect on clearance. In contrast, changes in intrinsic clearance and protein binding will affect the clearance of drugs with low extraction ratios, but changes in blood flow should have little effect.

**Renal Clearance.** Renal clearance of a drug results in its appearance as such in the urine; changes in the pharmacokinetic properties of drugs due to renal disease also may be explained in terms of clearance concepts. However, the complications that relate to filtration, active secretion, and reabsorption must be considered. The rate of filtration of a drug depends on the volume of fluid that is filtered in the glomerulus and the unbound concentration of drug in plasma, since drug bound to protein is not filtered. The rate of secretion of drug by the kidney will depend on the binding of drug to the proteins involved in active transport relative to that bound to plasma proteins, the degree of saturation of these carriers, the rate of transfer of the drug across the tubular membrane, and the rate of delivery of the drug to the secretory site. The influences of changes in protein binding, blood flow, and the number of functional nephrons are analogous to the examples given above for hepatic elimination.

## Distribution

**Volume of Distribution.** Volume is a second fundamental parameter that is useful in discussing processes of drug disposition. The volume of distribution ($V$) relates the amount of drug in the body to the concentration of drug ($C$) in the blood or plasma, depending upon the fluid measured. This volume does not necessarily refer to an identifiable physiological volume, but merely to the fluid volume that would be required to contain all of the drug in the body at the same concentration as in the blood or plasma:

$$V = \text{Amount of drug in body}/C \qquad (1\text{–}9)$$

The plasma volume of a typical 70-kg man is 3 liters, blood volume is about 5.5 liters, extracellular fluid volume outside the plasma is 12 liters, and the volume of total body water is approximately 42 liters. However, many drugs exhibit volumes of distribution far in excess of these values. For example, if 500 $\mu$g of digoxin were in the body of a 70-kg subject, a plasma concentration of approximately 0.7 ng/ml would be observed. Dividing the amount of drug in the body by the plasma concentration yields a volume of distribution for digoxin of about 700 liters, or a value ten times greater than the total body volume of a 70-kg man. In fact, digoxin, which is relatively hydrophobic, distributes preferentially to muscle and adipose tissue and to its specific receptors, leaving a very small amount of drug in the plasma. For drugs that are extensively bound to plasma proteins but that are not bound to tissue components, the volume of distribution will approach that of the plasma volume. In contrast, certain drugs have high volumes of distribution even though most of the drug in the circulation is bound to albumin, because these drugs are also sequestered elsewhere.

The volume of distribution may vary widely depending on the p$K_a$ of the drug, the degree of binding to plasma proteins, the partition coefficient of the drug in fat, the degree of binding to other tissues, and so forth. As mi expected, the volume of distribution for a given drug can change as a function of the patient's age, gender, disease, and body composition.

Several volume terms commonly are used to describe drug distribution, and they have been derived in a number of ways. The volume of distribution defined in equation 1–9 considers the body as a single homogeneous compartment. In this one-compartment model, all drug administration occurs directly into the central compartment and distribution of drug is instantaneous throughout volume ($V$). Clearance of drug from this compartment occurs in a first-order fashion, as defined in equation 1–2; that is, the amount of drug eliminated per unit time depends on the amount (concentration) of drug in the body compartment. Figure 1–5, *A* and equation 1–10 describe the decline of plasma concentration with time for a drug introduced into this compartment.

$$C = (\text{Dose}/V) \cdot exp(-kt) \qquad (1\text{–}10)$$

where $k$ is the rate constant for elimination of the drug from the compartment. This rate constant is inversely related to the half-life of the drug ($k = 0.693/t_{1/2}$).

For most drugs, the idealized one-compartment model discussed above does not describe the entire time course of the plasma concentration. That is, certain tissue reservoirs can be distinguished from the central compartment, and the drug concentration appears to decay in a manner that can be described by multiple exponential terms (*see* Figure 1–5, *B*).

***Rate of Drug Distribution.*** The multiple exponential decay observed for a drug that is eliminated from the body with first-order kinetics results from differences in the rates at which the drug equilibrates with tissue reservoirs. The rate of equilibration will depend upon the ratio of the perfusion of the tissue to the partition of drug into the tissue. In many cases, groups of tissues with similar perfusion/partition ratios all equilibrate at essentially the same rate, such that only one apparent phase of distribution (rapid initial fall of concentration, as in Figure 1–5, *B*) is seen. It is as though the drug starts in a "central" volume, which consists of plasma and tissue reservoirs that are in rapid equilibrium with it, and distributes to a "final" volume, at which point concentrations in plasma decrease in a log-linear fashion at rate $k$ (*see* Figure 1–5, *B*).

If the pattern or ratio of blood flows to various tissues changes within an individual or differs among individuals, rates of drug distribution to tissues also will change. However, changes in blood flow also may cause some tissues that were originally in the "central" volume to equilibrate sufficiently more slowly so as to appear only in the "final" volume. This means that central volumes will appear to vary with disease states that cause altered regional blood flow. After an intravenous bolus dose, drug concentrations in plasma may be higher in individuals with poor perfusion (*e.g.,* shock) than they would be if perfusion were better. These higher systemic concentrations may, in turn, cause higher concentrations (and greater effects) in tissues such as brain and heart whose usually high perfusion has ced by the altered hemodynamic state. Thus, the effect

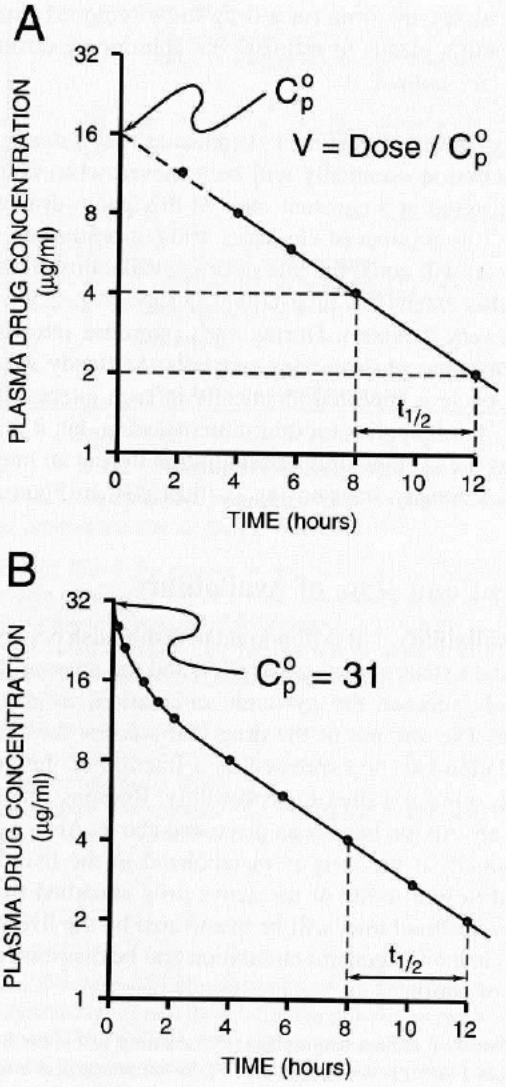


***Figure 1–5. Plasma concentration–time curves following intravenous administration of a drug (500 mg) to a 70-kg man.***

***A.*** In this example, drug concentrations are measured in plasma 2 hours after the dose is administered. The semilogarithmic plot of plasma concentration versus time appears to indicate that the drug is eliminated from a single compartment by a first-order process (equation 1–10) with a half-life of 4 hours ($k = 0.693/t_{1/2} = 0.173\ \text{h}^{-1}$). The volume of distribution ($V$) may be determined from the value of $C_p$ obtained by extrapolation to $t = 0$ ($C_p^o = 16$ µg/ml). Volume of distribution (equation 1–9) for the one-compartment model is 31.3 liters or 0.45 liter/kg ($V = \text{dose}/C_p^o$). The clearance for this drug is 92 ml/min; for a one-compartment model, $CL = k \cdot V$.

***B.*** Sampling before 2 hours indicates that, in fact, the drug follows multiexponential kinetics. The terminal disposition half-life is 4 hours, clearance is 103 ml/min (equation 1–4), $V_{area}$ is 28 liters (equation 1–11), and $V_{ss}$ is 25.4 liters. The initial or "central" distribution volume for the drug ($V_1 = \text{dose}/C_p^o$) is 16.1 liters. The example chosen indicates that multicompartment kinetics may be overlooked when sampling at early times is neglected. In this particular case, there is only a 10% error in the estimate of clearance when the multicompartment characteristics are ignored. For many drugs multicompartment kinetics may be observed for significant periods of time, and failure to consider the distribution phase can lead to significant errors in estimates of clearance and in predictions of the appropriate dosage.

of a drug at various sites of action can be variable, depending on perfusion of these sites.

***Multicompartment Volume Terms.*** Two different terms have been used to describe the volume of distribution for drugs that follow multiple exponential decay. The first, designated $V_{area}$, is calculated as the ratio of clearance to the rate of decline of concentration during the elimination (final) phase of the logarithmic concentration versus time curve:

$$V_{area} = \frac{CL}{k} = \frac{\text{Dose}}{k \cdot AUC} \tag{1–11}$$

The calculation of this parameter is straightforward, and the volume term may be determined after administration of a single dose of drug by intravenous or enteral routes (where the dose used must be corrected for bioavailability). However, another multicompartment volume of distribution may be more useful, especially when the effect of disease states on pharmacokinetics is to be determined. The

ume of distribution at steady state ($V_{ss}$) represents the volume in which a drug would appear to be distributed during steady state if the drug existed throughout that volume at the same concentration as that in the measured fluid (plasma or blood). Following intravenous dosing, calculation of $V_{ss}$ is more complicated than equation 1–11, but feasible (Benet and Galeazzi, 1979). It is more difficult to estimate $V_{ss}$ following enteral dosing. Although $V_{area}$ is a convenient and easily calculated parameter, it varies when the rate constant for drug elimination changes, even when there has been no change in the distribution space. This is because the terminal rate of decline of the concentration of drug in blood or plasma depends not only on clearance but also on the rates of distribution of drug between the central and final volumes. $V_{ss}$ does not suffer from this disadvantage. When using pharmacokinetics to make drug dosing decisions, the differences between $V_{area}$ and $V_{ss}$ usually are not clinically significant. Nonetheless, both are quoted in the Table of Pharmacokinetic Data in Appendix II, depending upon availability in the published literature.

## Half-Life

The half-life ($t_{1/2}$) is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%. For the simplest case, the one-compartment model (Figure 1–5, *A*), half-life may be determined readily and used to make decisions about drug dosage. However, as Figure 1–5, *B*, drug concentrations in plasma often follow a multiexponential pattern of decline; two or more half-life terms may thus be calculated.

In the past, the half-life that was usually reported corresponded to the terminal log-linear phase of elimination. However, as greater analytical sensitivity has been achieved, the lower concentrations measured appeared to yield longer and longer terminal half-lives. For example, a terminal half-life of 53 hours is observed for gentamicin (versus the 2- to 3-hour value in Appendix II), and biliary cycling is probably responsible for the 120-hour terminal value for indomethacin (as compared with the 2.4-hour half-life listed in Appendix II). The relevance of a particular half-life may be defined in terms of the fraction of the clearance and volume of distribution that is related to each half-life and whether plasma concentrations or amounts of drug in the body are best related to measures of response. The single half-life values given for each drug in Appendix II are chosen to represent the most clinically relevant half-life.

Early studies of pharmacokinetic properties of drugs in disease were compromised by their reliance on half-life as the sole measure of alterations of drug disposition. Only recently has it been appreciated that half-life is a derived parameter that changes as a function of both clearance and volume of distribution. A useful approximate relationship between the clinically relevant half-life, clearance, and volume of distribution at steady-state is given by:

$$t_{1/2} \cong 0.693 \cdot V_{ss}/CL \qquad (1\text{–}12)$$

Clearance is the measure of the body's ability to eliminate a drug. However, the organs of elimination can only clear drug from the blood or plasma with which they are in direct contact. As clearance decreases, due to a disease process, for example, half-life would be expected to increase. However, this reciprocal relationship is exact only when the disease does not change the volume of distribution. For example, the half-life of diazepam increases with increasing age; however, it is not clearance that changes as a function of age, but the volume of distribution (Klotz *et al.*, 1975). Similarly, changes in protein binding of the drug may affect its clearance as well as its volume of distribution, leading to unpredictable changes in half-life as a function of disease. The half-life of tolbutamide, for example, decreases in patients with acute viral hepatitis, exactly the opposite from what one might expect. The disease appears to modify protein binding in both plasma and tissues, causing no change in volume of distribution but an increase in total clearance, because higher concentrations of free drug are present (Williams *et al.*, 1977).

Although it can be a poor index of drug elimination, half-life does provide a good indication of the time required to reach steady state after a dosage regimen is initiated (*i.e.*, four half-lives to reach approximately 94% of a new steady state), the time for a drug to be removed from the body, and a means to estimate the appropriate dosing interval (*see* below).

**Steady State.** Equation 1–1 indicates that a steady-state concentration eventually will be achieved when a drug is administered at a constant rate. At this point, drug elimination (the product of clearance and concentration; equation 1–2) will equal the rate of drug availability. This concept also extends to intermittent dosage (*e.g.*, 250 mg of drug every 8 hours). During each interdose interval, the concentration of drug rises and falls. At steady state, the entire cycle is repeated identically in each interval. Equation 1–1 still applies for intermittent dosing, but it now describes the average drug concentration during an interdose interval. Steady-state dosing is illustrated in Figure 1–6.

## Extent and Rate of Availability

**Bioavailability.** It is important to distinguish between the rate and extent of drug absorption and the amount that ultimately reaches the systemic circulation, as discussed above. The amount of the drug that reaches the systemic circulation can be expressed as a fraction of the dose $F$, which often is called bioavailability. Reasons for incomplete absorption have been discussed above. Also, as noted previously, if the drug is metabolized in the liver or excreted in bile, some of the active drug absorbed from the gastrointestinal tract will be inactivated by the liver before it can reach the general circulation and be distributed to its sites of action.

Knowing the extraction ratio ($E$) for a drug across the liver (*see* equation 1–8), it is possible to predict the maximum oral availability ($F_{max}$), assuming hepatic elimination follows first-order processes:

$$F_{max} = 1 - E = 1 - (CL_{hepatic}/Q_{hepatic}) \qquad (1\text{–}13)$$

Thus, if the hepatic blood clearance for the drug is large relative to hepatic blood flow, the extent of availability will be low when it is given orally (*e.g.*, lidocaine). This decrease in availability is a function of the physiological site from which absorption takes place, and no modification of dosage form will improve the availability under conditions of linear kinetics.

When drugs are administered by a route that is subject to first-pass loss, the equations presented previously that contain the terms *dose* or *dosing rate* (equations 1–1, 1–4, 1–10, and 1–11) also must include the bioavailability term $F$, such that the available dose or dosing rate is used. For example, equation 1–1 is modified to:

$$F \cdot \text{Dosing rate} = CL \cdot C_{ss} \qquad (1\text{–}14)$$

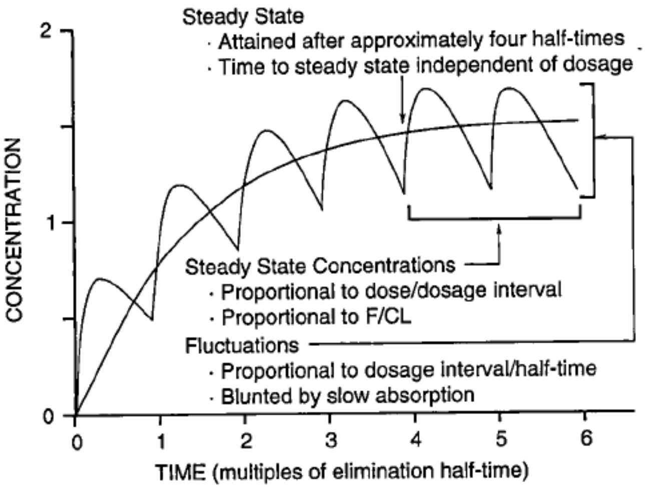


***Figure 1–6. Fundamental pharmacokinetic relationships for repeated administration of drugs.***

The blue line is the pattern of drug accumulation during repeated administration of a drug at intervals equal to its elimination half-time, when drug absorption is ten times as rapid as elimination. As the relative rate of absorption increases, the concentration maxima approach 2 and the minima approach 1 during the steady state. The black line depicts the pattern during administration of equivalent dosage by continuous intravenous infusion. Curves are based upon the one-compartment model.

Average concentration ($\overline{C}_{ss}$) when the steady state is attained during intermittent drug administration:

$$\overline{C}_{ss} = \frac{F \cdot \text{dose}}{CL \cdot T}$$

where $F$ = fractional bioavailability of the dose and $T$ = dosage interval (time). By substitution of infusion rate for $F \cdot \text{dose}/T$, the formula is equivalent to equation 1–1 and provides the concentration maintained at steady state during continuous intravenous infusion.

**Rate of Absorption.** Although the rate of drug absorption does not, in general, influence the average steady-state concentration of the drug in plasma, it may still influence drug therapy. If a drug is absorbed very rapidly (*e.g.*, a dose given as an intravenous bolus) and has a small central volume, the concentration of drug initially will be high. It will then fall as the drug is distributed to its final (larger) volume (*see* Figure 1–5, *B*). If the same drug is absorbed more slowly (*e.g.*, by slow infusion), it will be distributed while it is being given, and peak concentrations will be lower and will occur later. A given drug may act to produce both desirable and undesirable effects at several sites in the body, and the rates of distribution of drug to these sites may not be the same. The relative intensities of t

different effects of a drug may thus vary transiently when its rate of administration is changed.

## Nonlinear Pharmacokinetics

Nonlinearity in pharmacokinetics (*i.e.*, changes in such parameters as clearance, volume of distribution, and half-life as a function of dose or concentration of drug) usually is due to saturation of protein binding, hepatic metabolism, or active renal transport of the drug.

**Saturable Protein Binding.** As the molar concentration of drug increases, the unbound fraction eventually must also increase (as all binding sites become saturated). This usually occurs only when drug concentrations in plasma are in the range of tens to hundreds of micrograms per milliliter. For a drug that is metabolized by the liver with a low extraction ratio, saturation of plasma protein binding will cause both $V$ and clearance to increase as drug concentrations increase; half-life may thus remain constant (*see* equation 1–12). For such a drug, $C_{ss}$ will not increase linearly as the rate of drug administration is increased. For drugs that are cleared with high extraction ratios, $C_{ss}$ can remain linearly proportional to the rate of drug administration. In this case, hepatic clearance would not change, and the increase in $V$ would increase the half-time of disappearance by reducing the fraction of the total drug in the body that is delivered to the liver per unit time. Most drugs fall between these two extremes, and the effects of nonlinear protein binding may be difficult to predict.

**Saturable Metabolism.** In this situation, the Michaelis–Menten equation (equation 1–6) usually describes the nonlinearity. All active processes are undoubtedly saturable, but they will appear to be linear if values of drug concentrations encountered in practice are much less than $K_m$. When they exceed $K_m$, nonlinear kinetics is observed. The major consequences of saturation of metabolism are the opposite of those for saturation of protein binding. When both conditions are present simultaneously, they may virtually cancel each others' effects, and surprisingly linear kinetics may result; this occurs over a certain range of concentrations for salicylic acid.

Saturable metabolism causes first-pass metabolism to be less than expected (higher $F$), and there is a greater fractional increase in $C_{ss}$ than the corresponding fractional increase in the rate of drug administration. The latter can be seen most easily by substituting equation 1–6 into equation 1–1 and solving for the steady-state concentration:

$$C_{ss} = \frac{\text{Dosing rate} \cdot K_m}{v_m - \text{Dosing rate}} \tag{1–15}$$

As the dosing rate approaches the maximal elimination rate ($v_m$), the denominator of equation 1–15 approaches zero and $C_{ss}$ increases disproportionately. Fortunately, saturation of metabolism should have no effect on the volume of distribution; thus, as clearance decreases, the apparent half-life for elimination increases and the approach to the (disproportionate) new steady state is slow. However, the concept of "four half-lives to steady state" is not applicable for drugs with nonlinear metabolism in the usual range of clinical concentrations.

Phenytoin provides an example of a drug for which metabolism becomes saturated in the therapeutic range of concentrations (*see* Appendix II). $K_m$ is typically near the lower end of the therapeutic range ($K_m$ = 5 to 10 mg per liter). For some individuals, especially chil- be as low as 1 mg per liter. If, for such an individual, the target concentration is 15 mg per liter, and this is attained at a dosing rate of 300 mg per day, then, from equation 1–15, $v_m$ equals 320 mg per day. For such a patient, a dose 10% less than optimal (*i.e.,* 270 mg per day) will produce a $C_{ss}$ of 5 mg per liter, well below the desired value. In contrast, a dose 10% greater than optimal (330 mg per day) will exceed metabolic capacity (by 10 mg per day) and cause a long and slow but unending climb in concentration until toxicity occurs. Dosage cannot be controlled so precisely (less than 10% error). Therefore, for those patients in whom the target concentration for phenytoin is more than tenfold greater than the $K_m$, alternating inefficacious therapy and toxicity is almost unavoidable.

## Design and Optimization of Dosage Regimens

When long-term therapy is initiated, a pharmacodynamic question must be asked: What degree of drug effect is desired and achievable? If some effect of the drug is easily measured (*e.g.,* blood pressure), it can be used to guide dosage, and a trial-and-error approach to optimal dosage is both practical and sensible. Even in this ideal case, certain quantitative issues arise, such as how often to change dosage and by how much. These usually can be settled with simple rules of thumb based on the principles discussed (*e.g.,* change dosage by no more than 50% and no more often than every three to four half-lives). Alternatively, some drugs have very little dose-related toxicity, and maximum efficacy is usually desired. For these drugs, doses well in excess of the average required will both ensure efficacy (if this is possible) and prolong drug action. Such a "maximal dose" strategy typically is used for penicillins and most $\beta$-adrenergic blocking agents.

**Target Level.** For some drugs, the effects are difficult to measure (or the drug is given for prophylaxis), toxicity and lack of efficacy are both potential dangers, and/or the therapeutic index is narrow. In these circumstances doses must be titrated carefully, and a target-level strategy is reasonable. A desired (target) steady-state concentration of the drug (usually in plasma) is chosen, and a dosage is computed that is expected to achieve this value. Drug concentrations are subsequently measured, and dosage is adjusted if necessary to approximate the target more closely (*see also* Chapter 3).

To apply the target-level strategy, the therapeutic objective must be defined in terms of a desirable range for the $C_{ss}$, often called the therapeutic range. For drugs for which this can be done, such as theophylline and digoxin, the lower limit of the therapeutic range appears to be approximately equal to the drug concentration that produces about half of the greatest possible therapeutic effect. The upper limit of the therapeutic range (for drugs with such a limit) is fixed by toxicity, not by efficacy. In general, the upper limit of the therapeutic range is such that no more than 5% to 10% of patients will experience a toxic effect. For some drugs, this may mean that the upper limit of the range is no more than twice the lower limit. Of course, these figures can be highly variable, and some patients may benefit greatly from drug concentrations that exceed the therapeutic range, while others may suffer significant toxicity at much lower values. Barring more specific information, however, the target is usually chosen as the center of the therapeutic range.

**Maintenance Dose.** In most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion in order to maintain a steady-state concentration of drug in plasma within a given therapeutic range. Thus, calculation of the appropriate maintenance dosage is a primary goal. To maintain the chosen steady-state or target concentration, the rate of drug administration is adjusted such that the rate of input equals the rate of loss. This relationship was defined previously in equations 1–1 and 1–14 and is expressed here in terms of the desired target concentration:

$$\text{Dosing rate} = \text{Target} \cdot CL/F \tag{1–16}$$

If the clinician chooses the desired concentration of drug in plasma and knows the clearance and availability for that drug in a particular patient, the appropriate dose and dosing interval can be calculated.

***Example.*** A steady-state plasma concentration of theophylline of 15 mg per liter is desired to relieve acute bronchial asthma in a 68-kg patient. If the patient does not smoke and is otherwise normal except for the asthmatic condition, one can use the mean clearance given in Appendix II, that is, $0.65\ \text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. Because the drug is to be given as an intravenous infusion, $F = 1$:

$$\begin{aligned}\text{Dosing rate} &= \text{Target} \cdot CL/F\\ &= 15\ \mu\text{g/ml} \cdot 0.65\ \text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}\\ &= 9.75\ \mu\text{g} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}\\ &= 40\ \text{mg/h for a 68-kg patient}\end{aligned}$$

Since almost all intravenous preparations of theophylline are available as the ethylenediamine salt (aminophylline), which contains 85% theophylline, the infusion rate will be 47 mg per hour of aminophylline [(40 mg per hour)/(0.85)].

***Dosing Interval for Intermittent Dosage.*** In general, marked fluctuations in drug concentrations between doses are not beneficial. If absorption and distribution were instantaneous, fluctuation of drug concentrations between doses would be governed entirely by the drug's elimination half-life. If the dosing interval ($T$) was chosen to be equal to the half-life, then the total fluctuation would be twofold; this is usually a tolerable variation.

Pharmacodynamic considerations modify this. If a drug is relatively nontoxic, such that concentrations many times that necessary for therapy can be tolerated easily, the maximal dose strategy can be used, and the dosing interval can be much longer than the elimination half-life (for convenience). The half-life of penicillin G is less than 1 hour, but it is often given in very large doses every 6 or 12 hours.

For some drugs with a narrow therapeutic range, it may be important to estimate the maximal and minimal concentrations that will occur for a particular dosing interval. The minimal steady-state concentration $C_{ss,\,min}$ may be reasonably determined by the use of equation 1–17:

$$C_{ss,\,min} = \frac{F \cdot \text{dose}/V_{ss}}{1 - exp(-kT)} \cdot exp(-kT) \tag{1–17}$$

where $k$ equals 0.693 divided by the clinically relevant plasma half-life and $T$ is the dosing interval. The term $exp(-kT)$ is, in fact, the fraction of the last dose (corrected for bioavailability) that remains in the body at the end of a dosing interval.

For drugs that follow multiexponential kinetics and that are administered orally, the estimation of the maximal steady-state concentration $C_{ss,\,max}$ involves a complicated set of exponential constants for distribution and absorption. If these terms are ignored for multiple oral dosing, one may easily predict a maximal steady-state concentration by omitting the $exp(-kT)$ term in the numerator of equation 1–17 (*see* equation 1–18, below). Because of the approximation, the predicted maximal concentration from equation 1–18 will be greater than that actually observed.

***Example.*** When the acute asthmatic attack in the patient discussed above is relieved, the clinician might want to maintain the plasma concentration of theophylline at 15 mg per liter, with oral dosage at intervals of 6, 8, or 12 hours. The correct rate of drug administration, independent of consideration of the dosing interval, is 40 mg per hour for this patient, as calculated above, since the availability of theophylline from an oral dose is 100%. Thus, the appropriate intermittent doses would be 240 mg every 6 hours, 320 mg every 8 hours, or 480 mg every 12 hours. All of these regimens would yield the same average concentration of 15 mg per liter, but different maximal and minimal concentrations would obtain. For a 12-hour dosing interval, the following maximal and minimal concentrations would be predicted:

$$\begin{aligned} C_{ss,max} &= \frac{F \cdot \text{dose}/V_{ss}}{1 - exp(-kT)} \\ &= \frac{480 \text{ mg}/34 \text{ liters}}{0.65} = 21.7 \text{ mg/liter} \end{aligned} \tag{1–18}$$

$$\begin{aligned} C_{ss,min} &= C_{ss,max} \cdot exp(-kT) \\ &= (21.7 \text{ mg/liter}) \cdot (0.35) = 7.6 \text{ mg/liter} \end{aligned} \tag{1–19}$$

The calculations in equations 1–18 and 1–19 were performed assuming oral doses of 480 mg every 12 hours of a drug with a half-life of 8 hours ($k = 0.693/8 \text{ h} = 0.0866 \text{ h}^{-1}$), a volume of distribution of 0.5 liter/kg ($V_{ss} = 34$ liters for a 68-kg patient), and an oral availability of 1. Since the predicted minimal concentration, 7.6 mg per liter, falls below the suggested effective concentration and the predicted maximal concentration is above that suggested to avoid toxicity (*see* Appendix II), the choice of a 12-hour dosing interval is probably inappropriate. A more appropriate choice would be 320 mg every 8 hours or 240 mg every 6 hours; for $T = 6$ h, $C_{ss,max} = 17$ mg per liter; $C_{ss,min} = 10$ mg per liter. Of course the clinician must balance the problem of compliance with regimens that involve frequent dosage against the problem of periods when the patient may be subjected to concentrations of the drug that could be too high or too low.

**Loading Dose.** The "loading dose" is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly. The appropriate magnitude for the loading dose is:

$$\text{Loading dose} = \text{Target } C_p \cdot V_{ss}/F \tag{1–20}$$

A loading dose may be desirable if the time required to attain steady state by the administration of drug at a constant rate (four elimination half-lives) is long relative to the temporal demands of the condition being treated. For example, the half-life of lidocaine is usually more than 1 hour. Arrhythmias encountered after myocardial infarction obviously may be life threatening, and one cannot wait 4 to 6 hours to achieve a therapeutic concentration of lidocaine by infusion of the drug at the rate required to maintain this concentration. Hence, use of a loading dose of lidocaine in the coronary care unit is standard.

The use of a loading dose also has significant disadvantages. First, the particularly sensitive individual may be exposed abruptly to a toxic concentration of a drug. Moreover, if the drug involved has a long half-life, it will take a long time for the concentration to fall if the level achieved was excessive. Loading doses tend to be large, and they are often given parenterally and rapidly; this can be particularly dangerous if toxic effects occur as a result of actions of the drug at sites that are in rapid equilibrium with plasma.

**Individualizing Dosage.** To design a rational dosage regimen, the clinician must know $F$, $CL$, $V_{ss}$, and $t_{1/2}$, and have some knowledge about rates of absorption and distribution of the drug. Moreover, one must judge what variations in these parameters might be expected in a particular patient. Usual values for the important parameters and appropriate adjustments that may be necessitated by disease or other factors are presented in Appendix II. There is, however, unpredictable variation among normal individuals; for many drugs, one standard deviation in the values observed for $F$, $CL$, and $V_{ss}$ is about 20%, 50%, and 30%, respectively. This means that 95% of the time the $C_{ss}$

that is achieved will be between 35% and 270% of the target; this is an unacceptably wide range for a drug with a low therapeutic index. If values of $C_p$ are measured, one can estimate values of $F$, $CL$, and $V_{ss}$ directly, and this permits more precise adjustment of a dosage regimen. Such measurement and adjustment are appropriate for many drugs with low therapeutic indices (*e.g.,* cardiac glycosides, antiarrhythmic agents, anticonvulsants, theophylline, and others).

## Therapeutic Drug Monitoring

The major use of measured concentrations of drugs (at steady state) is to refine the estimate of $CL/F$ for the patient being treated (using equation 1–14 as rearranged below):

$$CL/F \text{ (patient)} = \text{Dosing rate}/C_{ss} \text{ (measured)} \qquad (1\text{–}21)$$

The new estimate of $CL/F$ can be used in equation 1–16 to adjust the maintenance dose to achieve the desired target concentration.

Certain practical details and pitfalls related to therapeutic drug monitoring should be kept in mind. The first of these concerns the time of sampling for measurement of the drug concentration. If intermittent dosing is used, when during a dosing interval should samples be taken? It is necessary to distinguish between two possible uses of measured drug concentrations in order to understand the possible answers. A concentration of drug measured in a sample taken at virtually any time during the dosing interval will provide information that may aid in the assessment of drug toxicity. This is one type of therapeutic drug monitoring. It should be stressed, however, that such use of a measured concentration of drug is fraught with difficulties because of interindividual variability in sensitivity to the drug. When there is a question of toxicity, the drug concentration can be no more than just one of many items that serve to inform the clinician.

Changes in the effects of drugs may be delayed relative to changes in plasma concentration because of a slow rate of distribution or pharmacodynamic factors. Concentrations of digoxin, for example, regularly exceed 2 ng/ml (a potentially toxic value) shortly after an oral dose, yet these peak concentrations do not cause toxicity; indeed, they occur well before peak effects. Thus, concentrations of drugs in samples obtained shortly after administration can be uninformative or even misleading.

When concentrations of drugs are used for purposes of adjusting dosage regimens, samples obtained shortly after administration of a dose are almost invariably misleading. The point of sampling during supposed steady state is to modify one's estimate of $CL/F$ and thus one's choice of dosage. Early postabsorptive concentrations do not reflect clearance; they are determined primarily by the rate of absorption, the central (rather than the steady-state) volume of distribution, and the rate of distribution, all of which are pharmacokinetic features of virtually no relevance in choosing the long-term maintenance dosage. When the goal of measurement is adjustment of dosage, the sample should be taken well after the previous dose—as a rule of thumb just before the next planned dose, when the concentration is at its minimum. There is an exception to this approach: some drugs are nearly completely eliminated between doses and act only during the initial portion of each dosing interval. If, for such drugs, it is questionable whether efficacious concentrations are being achieved, a sample taken shortly after a dose may be helpful. Yet, if another concern is that low clearance (as in renal failure) may cause accumulation of drug, concentrations measured just before the next dose will reveal such accumulation and are considerably more useful for this purpose than is knowledge of the maximal concentration. For such drugs, determination of both maximal and minimal concentrations is thus recommended.

A second important aspect of the timing of sampling is its relationship to the beginning of the maintenance dosage regimen. When constant dosage is given, steady state is reached only after four half-lives have passed. If a sample is obtained too soon after dosage is begun, it will not accurately reflect clearance. Yet, for toxic drugs, if one waits until steady state is ensured, the damage may have been done. Some simple guidelines can be offered. When it is important to maintain careful control of concentrations, one may take the first sample after two half-lives (as calculated and expected for the patient), assuming no loading dose has been given. If the concentration already exceeds 90% of the eventual expected mean steady-state concentration, the dosage rate should be halved, another sample obtained in another two (supposed) half-lives, and the dosage halved again if this sample exceeds the target. If the first concentration is not too high, one proceeds with the initial rate of dosage; even if the concentration is lower than expected, one usually can await the attainment of steady state in another two estimated half-lives and then proceed to adjust dosage as described above.

If dosage is intermittent, there is a third concern with the time at which samples are obtained for determination of drug concentrations. If the sample has been obtained just prior to the next dose, as recommended, concentration will be a minimal value, not the mean. However, as discussed above, the estimated mean concentration may be calculated by using equation 1–14.

If a drug follows first-order kinetics, the average, minimum, and maximum concentrations at steady state are linearly related to dose and dosing rate (*see* equations 1–14, –17, and –18). Therefore, the ratio between the measured and the desired concentrations can be used to adjust the dose:

$$\frac{C_{ss}(\text{measured})}{C_{ss}(\text{desired})} = \frac{\text{Dose(previous)}}{\text{Dose(new)}} \qquad (1\text{–}22)$$

Finally, for some drugs that are particularly difficult to manage, computer programs may be useful for the design of dosage regimens. Such programs, which take into account measured drug concentrations and individual factors such as those listed in Appendix II, are becoming increasingly available (Gabrielsson and Weiner, 1994).

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