a LANGE medical book

1989

Basic and Clinical Pharmacology

Fourth Edition

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Prentice-Hall International Inc.

Notice: Our knowledge in clinical sciences is constantly changing. As new information becomes available, changes in treatment and in the use of drugs become necessary. The authors and the publisher of this volume have taken care to make certain that the doses of drugs and schedules of treatment are correct and compatible with the standards generally accepted at the time of publication. The reader is advised to consult carefully the instruction and information material included in the package insert of each drug or therapeutic agent before administration. This advice is especially important when using new or infrequently used drugs.

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Preface

The goal of this book is to provide a complete pharmacology text for medical students and for students and practitioners in other health sciences. It also provides complete reference information for clinicians.

The Organization of the Fourth Edition

The information in this book is organized according to the sequence used by many pharmacology courses: basic principles; autonomic drugs; cardiovascular-renal drugs; drugs with important actions on smooth muscle; central nervous system drugs; drugs used to treat inflammation, gout, and diseases of the blood; endocrine drugs; chemotherapeutic drugs; toxicology; and special topics. This sequence provides students with the greatest opportunity to integrate the basic science they know with the pharmacology they are learning. However, chapters are designed to be used equally well in courses that present these topics in a different sequence. The chapters emphasize information about drug groups and prototypes rather than repetitive detail about individual drugs.

The Revision for the Fourth Edition

This edition is considerably revised to include pertinent new information and to connect the pharmacology information presented with the basic concepts of molecular biology, biochemistry, physiology, biophysics, and other health science that the student is already familiar with. For instance, the authors point out the dramatic progress that has been made in identifying transmitters and hormones, characterizing receptors, and understanding drug-receptor interaction, receptor-effector interaction, and second messenger signaling. Many of these developments are due to the application of techniques derived from molecular biology and biophysics. This widened perspective makes it easier for the student to understand the essentials of drug action despite the ever-increasing numbers of drugs and drug groups.

The Table of Contents is now divided into sections so that the student can see how the material is organized. All of the chapters are updated, and many redrawn and new figures are included to illustrate new concepts. New features include a section in Chapter 2 on receptor-effector coupling and signaling mechanisms based on the new understanding of drug mechanisms mentioned above. Chapter 5 now contains a section explaining "orphan drug" legislation and the new FDA rulings on testing investigative drugs. The sections on drug mechanism of action in many chapters are substantially revised to include new information about receptor subtypes, structure, and function. Also, appropriate chapters contain sections on important new drugs released through 1988. The chapters that deal with specific drug groups contain a significant new section called Preparations Available. These useful sections list all of the clinical products available for prescription writing, including their available dosage forms. Finally, the bibliographies now include important new material published through 1988. Despite the amount of information added, this edition is approximately the same length as the last because overlapping and nonpharmacologic material was carefully reduced.

Additional Sources of Information

Two additional sources of information may be helpful. *Pharmacology: A Review For Examinations,* 2nd edition (Appleton & Lange, 1989), provides a succinct review of pharmacology with sample examination questions and answers. It should be particularly valuable for students preparing for board-type examinations. *Clinical Pharmacology '88/'89* (Appleton & Lange, 1988) is a pocket-size reference to the properties, prescribing, and use of drugs on hospital wards and in outpatient practice. It is designed for students in clinical training, house staff, and practicing physicians.

I am pleased to note that the third edition of *Basic & Clinical Pharmacology* has been very well received and that translations into Spanish and Portuguese are now in their second editions. Translations into other languages are under way; contact the publisher for additional information. I also wish to acknowledge the continuing major contributions of the staff at Appleton & Lange.

Suggestions and comments about *Basic & Clinical Pharmacology* are always welcome. They may be sent to me at the Department of Pharmacology, Box 0450, S-1210, University of California, San Francisco, CA 94143-0450.

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Section I. Basic Principles

Introduction 1

Bertram G. Katzung, MD, PhD

Pharmacology can be broadly defined as the science dealing with interactions between living systems and molecules, especially chemicals introduced from outside the system. This definition thus includes **medical pharmacology**—the science of materials used to prevent, diagnose, and treat disease—as well as the important role played by chemicals in the environment that *cause* disease and the use of certain chemicals as molecular probes for the study of normal biochemistry and physiology. **Toxicology** is that branch of pharmacology that deals with the undesirable effects of chemicals in biologic systems.

The Nature of Drugs

What is or is not a **drug** can be broadly or narrowly defined. For our purposes, a drug will be any small molecule that, when introduced into the body, alters the body's function by interactions at the molecular level. There is clearly some overlap with endocrinology in this definition. This is as it should be, since hormones are properly considered drugs whether introduced from outside the body ("exogenous") in any amount or released internally in increased amounts by administration of a stimulant agent. In contrast to hormones, xenobiotics (xenos [Greek]: foreigner) are chemicals that are *not* synthesized in the living system but must be introduced into it from the outside. Poisons are drugs whether administered with criminal or suicidal intent or encountered inadvertently in the environment.

Drugs vary in molecular size. Molecules as small as carbon monoxide and lithium ion and as large as thrombolytic enzymes fall within the above functional definition. However, the great majority of drugs fall into the molecular weight range of 100–1000. There is a reason for this: As noted below, a drug is often introduced for practical reasons into a part of the body remote from the target tissue. To be absorbed and distributed to the target organ, the drug molecule must be capable of diffusion (or transport by carrier mechanisms). With some exceptions, molecules within the narrow range of MW 100–1000 are capable of convenient administration and efficient absorption and distribution.

Drugs vary in shape. The shape of a drug is important because the vast majority of drugs interact with specific sites—receptor sites—on macromolecules in the body. The shape of the receptor site determines what kinds of drug molecules may interact with it; the shape of the drug must be complementary to the shape of the receptor site to produce an optimum fit. While variation in shape is an obvious result of differences in the number, identity, and interconnections of the atoms that comprise the drug, more than 25% of the drugs in use are **chiral** molecules; they exist in stereoisomeric pairs. Just as right and left gloves are usually not interchangeable, members of chiral drug pairs usually differ markedly in their effects on the body and often differ in the way they are eliminated from the body.

Drugs also vary in their chemical nature. On the one hand, there are highly reactive alkylating agents such as mechlorethamine; on the other, "inert" anesthetic gases such as xenon. The various classes of organic compounds—carbohydrates, proteins, and lipids—are all represented. Many drugs are weak acids or weak bases. This fact has important implications for the way they are handled by the body, since the pH differences between different compartments of the body may alter the degree of ionization of such compounds (see below).

Drug-Body Interactions

The interactions between a drug and the biologic system are conveniently divided into 2 classes: **pharmacodynamic** interactions, the effects of the drug on the body; and **pharmacokinetic** interactions, the way in which the body handles the drug. The quantitative aspects of pharmacodynamics—the drug receptor concept and dose-response relationships—are discussed in Chapter 2. The principles of pharmacokinetics—absorption, distribution, metabolism, and elimination—are presented in Chapters 3 and 4. Some of the introductory concepts used in discussing these interactions are presented in this chapter.

Drug Permeation

As noted above, movements of drug molecules—into the body from the site of administration (absorption), between different parts of the body (distribution), and out of the body (excretion)—are important characteristics of any useful therapeutic agent. Because the body is protected from the outside world and is itself internally compartmentalized by mem-

brane barriers to the free movement of water and solute, permeation of drug molecules across membranes plays a role in all 3 of these processes.

There are 4 major mechanisms by which drugs move across barriers.

A. Aqueous Diffusion: This is a pathway of limited capacity across most barriers, eg, the epithelial lining of the surfaces of the body, such as the cornea, gut, and bladder. Because the epithelial cells in these tissues are connected by tight junctions, only molecules small enough (less than MW 100–150, eg, Li^+, methanol) to pass through very small aqueous pores permeate these barriers by the aqueous route. In contrast, most capillaries have very large pores between cells that allow molecules as large as MW 20,000–30,000 to pass. The capillaries of most of the brain lack these pores, but they are found in a few areas of the central nervous system: the pituitary gland, the pineal gland, the median eminence, the area postrema, and the choroid plexus.

B. Lipid Diffusion: Movement across cell membranes by solution in the lipids of the membrane, with passive transfer across the lipid driven by a concentration gradient, is one of the most important mechanisms of drug permeation. Obviously, a high degree of lipid solubility relative to aqueous solubility (often quantitated as the octanol/water or olive oil/water partition coefficient) will favor this mode of permeation. However, since drugs must first be in aqueous solution to gain access to the lipid membrane, too low a level of water solubility is undesirable.

The rate of diffusion (magnitude of flux) is determined by Fick's law of diffusion, which relates the flux (J) to the permeability coefficient (P), the area across which diffusion occurs (A), and the concentration gradient ($C_1 - C_2$):

$$J = P \times A \times (C_1 - C_2)$$

For lipid diffusion, P is large for nonpolar (lipid-soluble) drugs and very much smaller for polar molecules.

A great many drugs are weak acids or weak bases. Such molecules are relatively *more water-soluble when ionized (polar) and more lipid-soluble when un-ionized*. The pH of the environment will determine the degree of ionization of weak acids and bases according to the Henderson-Hasselbalch equation ("protonated" = combined with a proton, H^+):

$$\log\left(\frac{\text{Protonated form}}{\text{Unprotonated form}}\right) = pK_a - pH \qquad (1)$$

For weak acids, eg, phenobarbital,

$$HA \rightleftharpoons H^+ + A^- \qquad (2)$$

The pK_a of phenobarbital is 7.4 (Table 1–1). Therefore, if phenobarbital is being excreted in an acid urine, more of the drug will be protonated (un-ionized) and readily reabsorbable by permeation across the lipid membranes of renal tubular cells. In an alkaline urine, more of the drug will be dissociated (ionized), poorly soluble in lipid, and more rapidly excreted. The magnitude of this effect can be estimated by applying the Henderson-Hasselbalch equation (equation 1):

For pH 6.4:

$$\log\left(\frac{HA}{A^-}\right) = 7.4 - 6.4 = 1$$

$$\text{antilog}\,(1) = 10$$

Therefore, the ratio of readily reabsorbed (protonated) to poorly reabsorbed (dissociated) phenobarbital is 10 when the urine pH is 6.4.

For pH 8.0:

$$\log\left(\frac{HA}{A^-}\right) = 7.4 - 8.0 = -0.6$$

$$\text{antilog}\,(-0.6) = 0.25$$

Therefore, in alkaline urine, most of the phenobarbital is dissociated (charged) and therefore readily excreted. In treating a patient who has taken an overdose of phenobarbital, alkalinizing the urine is one method of hastening elimination of the drug.

For weak bases, eg, pyrimethamine, an antimalaria drug:

$$H^+ + RNH_2 \rightleftharpoons RN^+H_3 \qquad (3)$$

and, as before,

$$\log\left(\frac{\text{Protonated form}}{\text{Unprotonated form}}\right) = pK_a - pH \qquad (1)$$

The pK_a of pyrimethamine is 7.0 (Table 1–1). Therefore, at pH 8.0, the ratio of the protonated to the unprotonated form is 0.1; at pH 7.0, the ratio is 1; and at pH 6 it is 10. However, the protonated form of a base is the ionized, poorly lipid-soluble form. Thus, in contrast to phenobarbital, more of the pyrimethamine is in the more lipid-soluble form in alkaline environments than in acid ones. This relationship is illustrated in Fig 1–1.

Most weak bases used in pharmacology are substituted amines. Because the nitrogen atom can form bonds with one, 2, 3, or 4 carbon atoms, we can speak of primary, secondary, tertiary, and quaternary amines. Pyrimethamine is a primary amine, since only one of the nitrogen bonds is to a carbon atom. Secondary and tertiary amines can also acquire a proton and become charged, as in the example given above. Quaternary amines, on the other hand, are permanently charged, since the carbon-nitrogen bond is not subject to change by physiologic pH alterations.

The degree of ionization of weak electrolytes is not the only factor that influences its lipid solubility, but it is especially important in those body compartments in which the pH may change. For instance, the gastric pH may vary between 1.5 and 7 and the pH of the

Table 1–1. Ionization constants of some common drugs.

Drug	pK_a[1]	Drug	pK_a[1]	Drug	pK_a[1]
Weak acids		**Weak bases (cont'd)**		**Weak bases (cont'd)**	
Acetaminophen	9.5	Amiloride	8.7	Methadone	8.4
Acetazolamide	7.2	Amphetamine	9.8	Methamphetamine	10.0
Ampicillin	2.5	Atropine	9.7	Methyldopa	10.6
Aspirin	3.5	Bupivacaine	8.1	Methysergide	6.6
Chlorothiazide	6.8, 9.4[2]	Chlordiazepoxide	4.6	Metoprolol	9.8
Chlorpropamide	5.0	Chloroquine	10.8, 8.4[2]	Morphine	7.9
Cromolyn	2.0	Chlorpheniramine	9.2	Nicotine	7.9, 3.1[2]
Ethacrynic acid	3.5	Chlorpromazine	9.3	Norepinephrine	8.6
Furosemide	3.9	Clonidine	8.3	Pentazocine	9.7
Ibuprofen	4.4, 5.2[2]	Cocaine	8.5	Phenylephrine	9.8
Levodopa	2.3	Codeine	8.2	Physostigmine	7.9, 1.8[2]
Methotrexate	4.8	Cyclizine	8.2	Pilocarpine	6.9, 1.4[2]
Methyldopa	2.2, 9.2[2]	Desipramine	10.2	Pindolol	8.8
Penicillamine	1.8	Diazepam	3.3	Procainamide	9.2
Pentobarbital	8.1	Dihydrocodeine	8.8	Procaine	9.0
Phenobarbital	7.4	Diphenhydramine	9.0	Promazine	9.4
Phenytoin	8.3	Diphenoxylate	7.1	Promethazine	9.1
Propylthiouracil	8.3	Ephedrine	9.6	Propranolol	9.4
Salicylic acid	3.0	Epinephrine	8.7	Pseudoephedrine	9.8
Sulfadiazine	6.5	Ergotamine	6.3	Pyrimethamine	7.0
Sulfapyridine	8.4	Fluphenazine	8.0, 3.9[2]	Quinidine	8.5, 4.4[2]
Theophylline	8.8[2]	Guanethidine	11.4, 8.3[2]	Scopolamine	8.1
Tolbutamide	5.3	Hydralazine	7.1	Strychnine	8.0, 2.3[2]
Warfarin	5.0	Imipramine	9.5	Terbutaline	10.1
Weak bases		Isoproterenol	8.6	Thioridazine	9.5
Albuterol (salbutamol)	9.3	Kanamycin	7.2	Tolazoline	10.6
Allopurinol	9.4, 12.3[2]	Lidocaine	7.9		
Alprenolol	9.6	Metaraminol	8.6		

[1] The pK_a is that pH at which the concentrations of the ionized and un-ionized forms are equal.
[2] More than one ionizable group.

urine between 5.5 and 8. For drugs that have moderately high lipid solubility in the un-ionized form (and that therefore permeate very readily), changes of pH of this magnitude can have considerable clinical significance. For example, phenobarbital is cleared 7 times more rapidly into alkaline urine than into acid urine. Mecamylamine, an antihypertensive drug and a weak base, is cleared almost 80 times more rapidly into acidic than into alkaline urine.

In contrast, the clearance of some weak acids and bases is not significantly influenced by urine pH. An example is penicillin, which is very water-soluble in both ionized and un-ionized forms and is actively secreted into the urine. It is, therefore, cleared very rapidly regardless of urine pH.

C. Via Special Carriers (Facilitated Diffusion): A few classes of drugs are transported by special carriers in the membranes of cells. Such carriers include those for amino acids in the "blood-brain barrier" and those for weak acids in the proximal convoluted tubule of the kidney.

D. Pinocytosis (Receptor-Mediated Endocytosis): Drugs of exceptionally large size (over MW 1000) enter cells primarily by pinocytosis—the process of engulfing extracellular material within membrane vesicles. This is of importance for some drugs, most of them polypeptides.

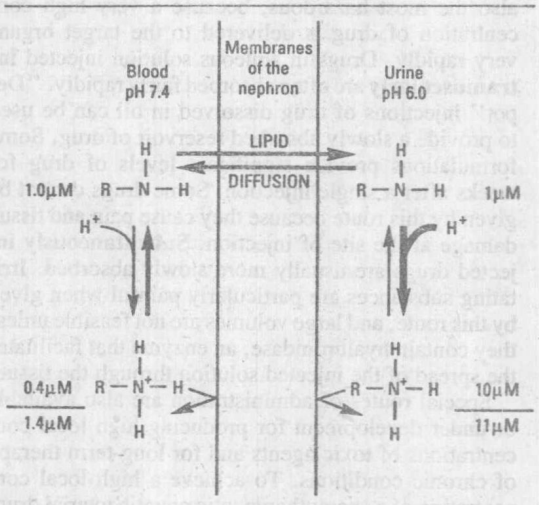

Figure 1–1. Trapping of a weak base (pyrimethamine) in the urine when the urine is more acidic than the blood. In the hypothetical case illustrated, the diffusible uncharged form of the drug has equilibrated across the membrane but the total concentration (charged plus uncharged) in the urine is almost 8 times higher than in the blood.

Factors Influencing Permeation

For most mechanisms of permeation, the rate of drug transfer is a function of the surface area available for transfer and, in the case of a passive process, of the concentration gradient driving it, as illustrated by Fick's law. Thus, transfer across the lipid barrier of organs with very large surface areas (lung, small in-

testine) is usually much faster than across small areas (stomach). The concentration gradient depends upon processes on both sides of the membrane. In a typical example of drug absorption from a site of subcutaneous administration, the amount of drug administered will determine the concentration on one side (the gradient source). The rate of removal of drug will determine the concentration on the other side (the gradient sink). Thus, a high blood flow will rapidly replace blood in which drug has dissolved with blood containing no drug, thereby maintaining a high concentration gradient. Vasodilator substances are typically absorbed very rapidly because they increase blood flow, whereas vasoconstrictor drugs are absorbed more slowly because they decrease flow.

Absorption of Drugs Into the Body

Use of a drug almost always involves transfer of the agent into the bloodstream. Exceptions include topical application for local effect on the skin or mucous membranes and oral administration of drugs that act from within the intestinal lumen such as antacids and some laxatives. However, even when the site of therapeutic action is in one of these locations, absorption into the bloodstream may occur and may have undesirable effects.

In addition to the factors described above that affect drug permeation, absorption into the blood is significantly influenced by the **route of administration.** In addition to the intravenous route, which bypasses the absorption process, the important routes of administration are oral, inhalational, topical, transdermal, subcutaneous, intramuscular, and buccal or sublingual. Less commonly, the intra-arterial, intrathecal, and rectal routes may be used.

The **oral route** is most commonly used because of its convenience and, for most drugs, efficiency of absorption. The large surface area of the gastrointestinal tract, the mixing of its contents, and the differences in pH at different levels favor effective absorption of drugs given in this way. However, the acid and enzymes secreted by the patient and the biochemical activity of the resident microbiologic flora also have the capacity to destroy some drugs before they are absorbed. Some penicillins are ineffective when given orally because they are rapidly inactivated by gastric acid. Polypeptide hormones such as insulin are hydrolyzed in the intestine. Such drugs must be given **parenterally** (by a nongastrointestinal route).

Because the gut is lined by epithelium with tight junctions, absorption of most drugs is by lipid diffusion. Thus, the basic rules of lipid permeation described above apply.

The **inhalational route** of administration, in addition to its obvious role in the use of gaseous anesthetics and other therapeutic gases, can be used for pharmacologic agents that vaporize readily, eg, amyl nitrite, and for drugs that can be dispersed in an aerosol of fine aqueous droplets, eg, certain ergot derivatives. Because of the very large surface area of the alveolar membrane and the high blood flow through the lungs, therapeutic gases of suitable solubility characteristics are rapidly absorbed from the lungs.

The airway itself is an important target of drugs used in asthma; the use of aerosols for delivery to the bronchi constitutes a type of topical administration.

The **topical route** includes application, for local effect, to the skin, the eye, the nose and throat, and the vaginal surface. (Drugs are occasionally used topically in the rectum for their anti-inflammatory effect. More often, the rectal route is used as an alternative to oral administration, for systemic effects.) The **transdermal route** utilizes application of drugs to the skin for systemic effects. Prolonged blood levels of some drugs can be achieved by this method because they are slowly absorbed. The skin constitutes a multilayered lipid barrier with special pharmacokinetic features that are discussed in Chapter 63. The basic principles of lipid permeation apply to the skin and to the other body surfaces mentioned above.

The **buccal route** is an important one for drugs that must be self-administered but are too rapidly inactivated by the liver to be useful after ingestion. Some drugs are so rapidly metabolized by the liver that when absorbed from the stomach and small intestine into the portal circulation they are more than 90% inactivated before reaching the systemic circulation. Blood flow through the buccal mucosa is high, and venous drainage is into systemic veins, not the portal circulation. Therefore, drugs such as nitroglycerin are effective in much lower dosage when placed under the tongue than when swallowed.

When drugs must be given by **injection,** several options are available. The **intravenous route** is the most direct and bypasses the absorption barriers. It is also the most hazardous, because a very high concentration of drug is delivered to the target organs very rapidly. Drugs in aqueous solution injected **intramuscularly** are often absorbed fairly rapidly. "Depot" injections of drug dissolved in oil can be used to provide a slowly absorbed reservoir of drug. Some formulations provide significant levels of drug for weeks after a single injection. Some drugs cannot be given by this route because they cause pain and tissue damage at the site of injection. **Subcutaneously** injected drugs are usually more slowly absorbed. Irritating substances are particularly painful when given by this route, and large volumes are not feasible unless they contain hyaluronidase, an enzyme that facilitates the spread of the injected solution through the tissue.

Special routes of administration are also available or under development for producing high local concentrations of toxic agents and for long-term therapy of chronic conditions. To achieve a high local concentration of a chemotherapeutic or antibacterial drug, **intra-arterial** or **intrathecal** injections can be given for acute or intermittent treatment. If continuous therapy is required, reservoirs of drug together with the necessary intra-arterial or intrathecal catheter can be surgically implanted near the target organ. These tech-

niques permit the use of much higher concentrations of drug in the target tissue than can be tolerated by the rest of the body. Long-term therapy with drugs that must normally be injected, eg, insulin, can also be carried out with implantable reservoirs. Such reservoirs may be equipped with radio frequency-controlled pumps to permit regulation of the rate of infusion. However, at the present time, such devices appear to offer little or no advantage over traditional intermittent injection techniques.

Distribution of Drugs Within the Body

Once a drug has been absorbed into the blood, it may be distributed to different physical compartments of the body (Table 1–2). If avidly bound to plasma proteins, it may remain in the vascular compartment until eliminated. Small water-soluble molecules may be freely distributed in the total body water. Drugs that are highly lipid-soluble (eg, DDT) are ultimately distributed to fat. Drugs that are not tightly bound to cells or proteins within the blood leave the vascular compartment, at a rate and to an extent governed by the permeability principles outlined above. Certain ions, especially the heavy metals and fluoride, are slowly sequestered in bone.

Such compartments of the body, since they constitute actual physical entities, may be considered *real* volumes of potential distribution. However, many drugs are not simply dissolved in these volumes but bind to cell surfaces and intercellular macromolecules. If the volume in which a drug is dissolved is computed by dividing the total amount of drug present in the body by the measured plasma concentration, the *apparent* volume of distribution is obtained. Because some drugs are almost 100% bound by tissue structures, leaving only a small amount in solution, the apparent volume of distribution may be extremely large—much larger than the total volume of the body (Chapter 3). Although the apparent volume of distribution is obviously an abstract rather than a real entity, it is nevertheless more useful than the real volume of distribution for purposes of pharmacokinetic calculation.

Table 1–2. Physical volumes (in L/kg) of examples of body compartments into which drugs may be distributed.

Compartment and Volume	Examples
Total body water (0.6 L/kg[1])	Small water-soluble molecules: eg, ethanol.
Extracellular water (0.2 L/kg)	Larger water-soluble molecules: eg, mannitol.
Blood (0.08 L/kg); plasma (0.04 L/kg)	Strongly plasma protein-bound molecules and very large molecules: eg, heparin.
Fat (0.2–0.35 L/kg)	Highly lipid-soluble molecules: eg, DDT.
Bone (0.07 L/kg)	Certain ions: eg, lead, fluoride.

[1] An average figure. Total body water in a young lean male might be 0.7 L/kg; in an obese woman, 0.5 L/kg.

The most important of the factors that determine drug distribution are protein binding, blood flow, membrane permeation, and tissue solubility.

In the blood, drugs may bind to albumin and several other serum proteins. The degree to which this occurs is usually measured as the percentage of total drug in the blood that is not dialyzable, ie, bound to large molecules (Table 3–1). Binding sites on these molecules are sometimes referred to as **inert binding sites** to differentiate them from **receptor binding sites,** since binding to albumin brings about no specific pharmacologic response, whereas (by definition) binding to the drug receptor alters the function of the cell that contains the receptor site. Binding to nonreceptor proteins may also take place outside the vascular compartment and may account for a significant fraction of the total drug in the body.

Drug molecules bound to inert binding sites are not available for diffusion or interaction with receptors. They are, however, in equilibrium with free drug, so that alterations in the concentration of free drug will result in changes in the amount (but not the percentage) bound.

Nonreceptor protein binding sites are not very specific—eg, many weak acids with different pharmacologic effects bind to the same or closely related plasma protein sites. Therefore, different drugs may compete for the same binding sites. This can have important consequences if a high percentage of a potent drug ("A") is bound, since the binding sites must be loaded to achieve a therapeutic concentration of free drug in the plasma. Addition of a second drug ("B") that competes for the same inert binding site (but not the receptor site) may cause a marked increase in the concentration of free "A" and thus precipitate toxicity. This and other types of pharmacokinetic drug interaction are described in Appendix I.

Blood flow determines how rapidly drug molecules are delivered to a given tissue and how effectively the concentration gradient between blood and tissue is maintained. Therefore, drugs equilibrate rapidly between the blood and organs with a high blood flow (Table 1–3). If the drug is very soluble or bound in the cells of these organs—eg, lipid-soluble drugs in the brain—then a very high concentration may be achieved at the steady state. Conversely, if an organ is sufficiently massive, eg, skeletal muscle, large amounts of drug may be distributed to it without ever reaching a very high concentration.

Elimination of Drugs From the Body & Termination of Drug Effect

Termination of drug effect is sometimes dependent upon excretion from the body. More commonly, termination of effect is the result of **biotransformation** to inactive products that are then excreted. A few drugs are given in a pharmacologically inactive ("pro-

Table 1–3. Blood flow to some important tissues of the body (based on a 70-kg human).

Tissue	Mass (kg)	Blood Flow (mL/min)	Flow (Percent of Cardiac Output)
Brain	1.4	750	13.9
Heart	0.3	250	4.7
Liver	2.9	1500	27.8
Kidneys	0.3	1260	23.3
Skeletal muscle	34.4	840	15.6
Skin	4.0	462	8.6
Placenta and fetus (term)	3.8	500	9
Whole body	70	5400	100

drug") form and metabolized into another form that is pharmacologically active. Therefore, drug excretion and drug metabolism must be considered separately.

The major organs for drug excretion are the kidneys, the liver, the gastrointestinal tract, and the lungs. Other minor routes of drug excretion are sweat and milk.

A. Kidneys: Drugs may be excreted by the kidneys by 2 processes, glomerular filtration and tubular secretion, and may also be reabsorbed, usually by passive diffusion. Glomerular filtration is a passive, nonsaturable process that removes molecules up to the size of small proteins. Therefore, drugs that are effectively bound to plasma protein are poorly filtered; and conversely, drugs that are not bound are cleared from the blood at a rate approximately equal to creatinine clearance (Chapter 3). Some drugs are actively secreted by special mechanisms located in the mid segment of the proximal convoluted tubule. Drugs that are weak acids, including many diuretic drugs, are secreted in this manner and may compete with endogenous acids such as uric acid for the carrier. Active secretion is a saturable process.

Once in the tubular urine, the drug is exposed to the lipid membrane of the nephron; highly lipid-soluble molecules will be rapidly reabsorbed; more water-soluble ones are likely to be excreted. Metabolism of many drugs results in a less lipid-soluble product (Chapter 4); such metabolites are less likely than the parent drug to be reabsorbed from the tubular lumen.

B. Liver: The liver is the most important organ for drug metabolism. Bile may contain higher concentrations of metabolites than of the parent molecule, especially if the metabolite is sufficiently polar to be reabsorbed poorly from bile. A few drugs appear to be actively secreted into the bile, eg, certain cardiac glycosides, antibiotics, and quaternary ammonium cholinergic blocking agents.

Drugs and their metabolites that are secreted into bile are carried by the biliary ducts and the common duct to the duodenum. Some drug may then be absorbed from the lumen of the intestine and appear again unchanged in the blood. This recycling of drug is termed **enterohepatic circulation.**

C. Gastrointestinal Tract: The walls of the stomach and intestines constitute large lipid membranes across which drugs can be transferred from blood to lumen. This passive diffusion is occasionally of importance when a weakly basic drug is present in very high concentration in the blood, eg, after self-administration of a large dose of morphine. Any morphine that diffuses into the acidic environment of the stomach would be almost 100% ionized (pK_a 7.9, pH 1.5–2.5) and poorly reabsorbed. Such trapped drug could then be removed by lavage. (If the morphine were not removed from the stomach, it would pass into the more alkaline environment of the intestine and be promptly reabsorbed.)

D. Lungs: The lungs are the most important route of excretion of gaseous anesthetics but a relatively unimportant route for most other drugs.

E. Minor Routes: Inconsequential amounts of drugs are excreted by the sweat and salivary glands. Similarly, the amount of drug excreted in milk is usually a small fraction of the total excreted. However, for the nursing infant, the drug in the milk may constitute a significant dose (Chapter 61).

History of a Single Administration of a Drug

As will be emphasized in Chapters 2 and 3, the most important factor determining the intensity of pharmacologic response is the concentration of drug at the receptor sites in the target tissue. It would be desirable to monitor this concentration to guide the adjustment of dosage, interpretation of treatment failure, etc, but direct tissue measurements are not often feasible in clinical practice. Therefore, blood (or plasma) concentrations are usually measured when pharmacokinetic studies are done.

The pharmacokinetic history of a drug dose, determined by repeatedly measuring its blood concentration after a single administration, provides useful information for developing a concept or "model" about how the body handles the drug. In their simplest form, such models can be thought of as systems of compartments into which the drug is placed at the time of administration or into which it diffuses. Fig 1–2 illustrates these concepts. For many drugs, the history of concentration in the blood is fairly well predicted by a 2-compartment model like that shown in Fig 1–2D. An example of 2-compartment behavior by a real drug is shown in Fig 1–3. Many other drugs exhibit more complex curves when analyzed in this way. A few drugs display simpler kinetic behavior. For example, a drug that is retained within the vascular compartment does not manifest a distribution phase. If such a drug were to enter the body and be neither metabolized nor excreted, it might produce the graph shown in Fig 1–2A.

Drug Groups

The proper use of a drug requires an understanding of its pharmacokinetic properties and its pharmacodynamic interactions. To learn each pertinent fact about each of the many hundreds of drugs mentioned