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TEXTBOOK OF PHARMACOLOGY

药 理 学

Original Editors

- Bertram G.Katzung
- Joel G.Hardman

Lee E.Limbird

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Chief Editor of Adaptation Edition

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Preface for Adaptation Edition

This book is designed to provide a complete, authoritative, current, and readable pharmacology textbook for medical students in China. Based on the domestic and foreign pharmacology textbooks, this book inherited the tradition of pharmacology education in China and adopted experience of training in other countries.

Information is organized according to the sequence used in many pharmacology courses: basic principles; autonomic drugs; drugs that act in the central nervous system; cardiovascular-renal drugs; drugs for digestive disorders and respiratory disorders and acting on the uterine smooth muscle; endocrine drugs; autocoids and anti-autocoid drugs; drugs that acting on the blood and the blood-forming organs, drugs that act in the immune system; and chemotherapeutic drugs. Within each chapter, emphasis is placed on discussion of drug groups and prototypes rather than offering repetitive detail about individual drugs.

Major features that make this book especially useful to professional students include sections that specifically address the clinical choice and use of drugs in patients and the monitoring of their effects-in other words. Clinical pharmacology is an integral part of this text. The book also offers special features that make it useful to house officers and practicing clinicians.

A English-China vocabulary is included in the appendix of this book, which can help students to grasp new words and promote their interests of learning English of pharmacology.

This book a reedited edition of the "Basic & Clinical Pharmacology, 9th edition", oringilly edited by Professor Bertram G. Katzung, MD, PhD and published by Lange Medical Books/McGraw-Hill in 2004. In the same time, another important related source of information is: Goodman & Gilman's the Pharmacological Basis of Therapeutics, 10th edition (McGraw-Hill, 2001).

I wish to acknowledge the ongoing efforts of my contributing authors, of the the major contributions of my assistant Dr. Wang Saiying , at Institute of Clinical Pharmacology, Central South University, and of our editors, of staff at Science Press and Lange Medical Books/McGraw-Hill.

Suggestions and comments about this book are always welcome. They may be sent to me at the Institute of Clinical Pharmacology, Central South University, 110 Xiangya Road, Changsha, Hunan 410078, China.

Zhou Honghao , MD

Changsha
February, 2006

改编版前言

这是一本具有系统性、权威性、先进性和适用性的英文教材，供国内医学院校学生双语学习使用。本着继承国内药理学教学传统，同时吸收国外经验的宗旨，本书章节是在沿用国内药理学同类教科书基础上，参照国外药理学教科书而编写的。

本书涉及的章节包括：总论，作用于外周神经的药物，作用于中枢神经系统的药物，作用于心血管和肾脏的药物，作用于消化、呼吸系统和子宫的药物，作用于内分泌系统的药物，作用于自体活性物质的药物，作用于血液系统的药物，作用于免疫系统的药物以及化学治疗药物。在编写中特别注意到内容新颖，材料精选，深入浅出，着重介绍了各个章节具有代表的典型药物，而不是一味地对个别药物做累赘的叙述。

本教材特色在于具有非常鲜明的临床指导意义，不仅适用于我国医学生，也可用于临床医生和其他专业人员学习、参考。

本教材在书后附上了关于本书重要名词的中英文对照，有利于提高学生的英文药理专业的兴趣和词汇的掌握。

在此感谢参与本书编写的各位作者，感谢我的助手中南大学临床药理学研究所的汪赛赢老师以及科学出版社和麦格劳-希尔公司为本书出版所给予的热情支持！

周宏灏

2006 年 2 月，长沙

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CONTENTS

SECTION I
Basic Principles

Chapter 1 Introduction

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

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

Chapter 2 Pharmacokinetics

The Dynamics of Drug Absorption, Distribution, and Elimination

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

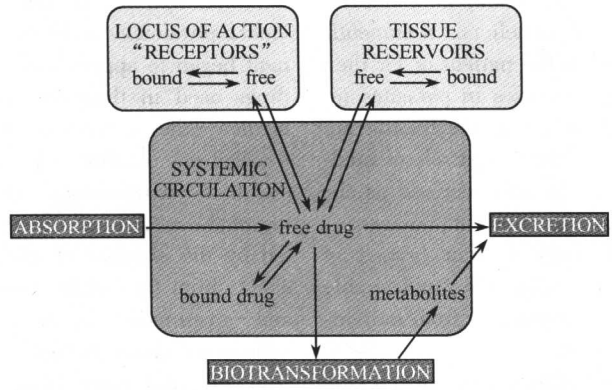

Figure 2-1 Schematic representation of the interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its locus of action.

PHYSICOCHEMICAL FACTORS IN TRANSFER OF DRUGS ACROSS MEMBRANES

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

Cell Membranes

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

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

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

Passive Membrane Transport

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

Weak Electrolytes and Influence of PH

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

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

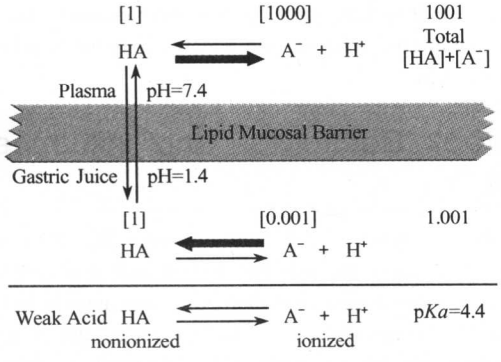

Figure 2-2 Influence of pH on the distribution of a weak acid between plasma and gastric juice, separated by a lipid barrier.

Carrier-Mediated Membrane Transport

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

DRUG ABSORPTION, BIOAVAILABILITY, AND ROUTES OF ADMINISTRATION

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

Oral (Enteral) Versus Parenteral Administration

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

Oral Ingestion

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

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

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

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

Controlled-Release Preparations

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

Sublingual Administration

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

Rectal Administration

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

Parenteral Injection

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

Intravenous

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

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

Topical Application

Mucous Membranes

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

Skin

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

Eye

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

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

DISTRIBUTION OF DRUGS

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

Plasma Proteins

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

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

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