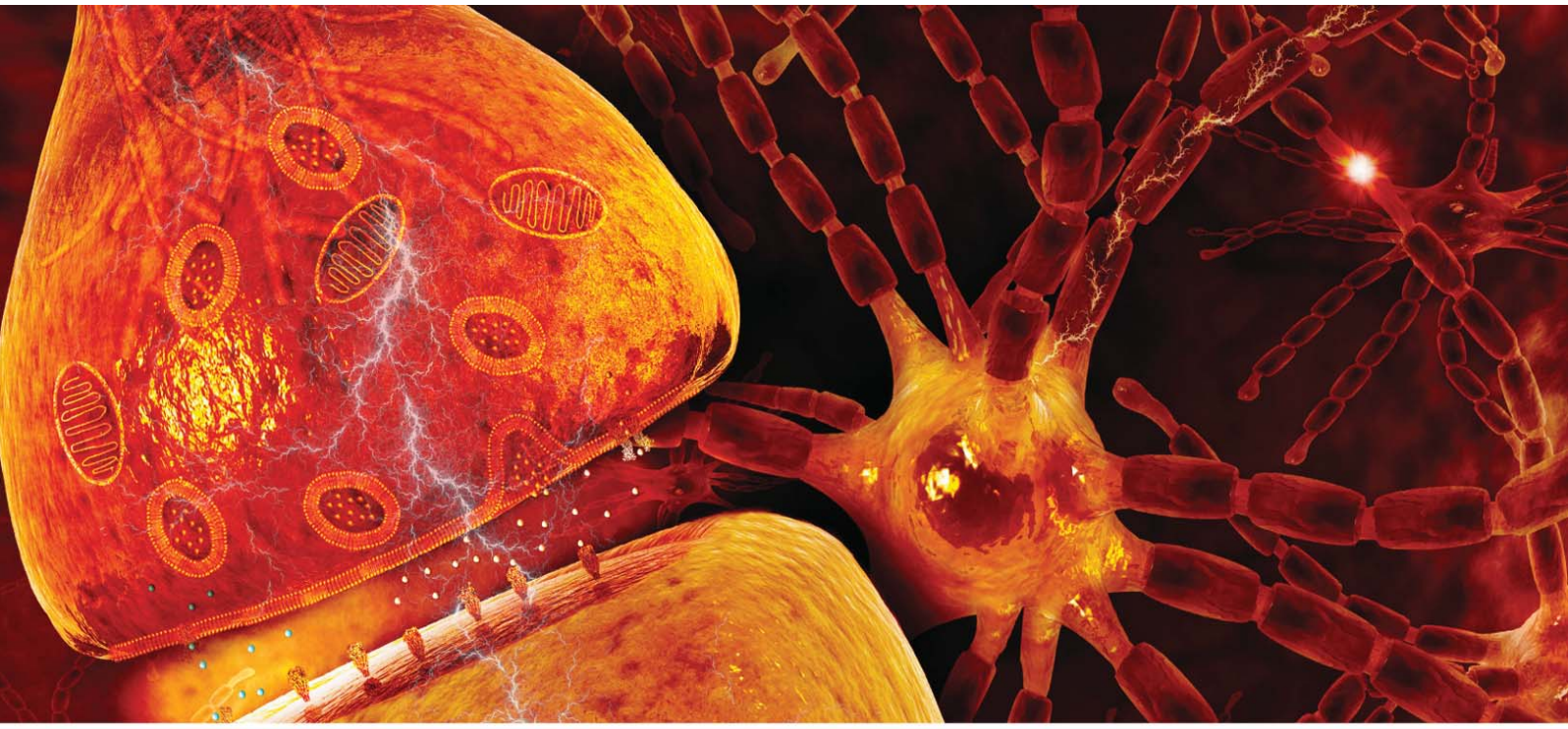

KATZUNG & TREVOR'S Pharmacology

EXAMINATION & BOARD REVIEW

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Katzung & Trevor's Pharmacology Examination & Board Review

Eleventh Edition

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Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Contents

Preface

This book is designed to help students review pharmacology and to prepare for both regular course examinations and board examinations. The eleventh edition has been revised to make such preparation as active and efficient as possible. As with earlier editions, rigorous standards of accuracy and currency have been maintained in keeping with the book's status as the companion to the *Basic & Clinical Pharmacology* textbook. This review book divides pharmacology into the topics used in most courses and textbooks. Major introductory chapters (eg, autonomic pharmacology and CNS pharmacology) are included for integration with relevant physiology and biochemistry. The chapter-based approach facilitates use of this book in conjunction with course notes or a larger text. We recommend several strategies to make reviewing more effective (**Appendix I** contains a summary of learning and test-taking strategies that most students find useful).

First, each chapter has a short discussion of the major concepts that underlie its basic principles or the specific drug group, accompanied by explanatory figures and tables. The figures are in full color and some are new to this edition. Students are advised to read the text thoroughly before they attempt to answer the study questions at the end of each chapter. If a concept is found to be difficult or confusing, the student is advised to consult a regular textbook such as *Basic & Clinical Pharmacology*, 13th edition.

Second, each drug-oriented chapter opens with an "**Overview**" that organizes the group of drugs visually in diagrammatic form. We recommend that students practice reproducing the overview diagram from memory.

Third, a list of **High Yield Terms to Learn** and their definitions is near the front of most chapters. Make sure that you are able to define those terms.

Fourth, many chapters include a "**Skill Keeper**" question that prompts the student to review previous material and to see links between related topics. We suggest that students try to answer Skill Keeper questions on their own before checking the answers that are provided at the end of the chapter.

Fifth, each of the sixty-one chapters contains up to ten **sample questions** followed by a set of answers with explanations. For most effective learning, you should take each set of sample questions as if it were a real examination. After you have answered every question, work through the answers. When you are analyzing the answers, make sure that you understand why each choice is either correct or incorrect.

Sixth, each chapter includes a **Checklist** of focused tasks that you should be able to do once you have finished the chapter.

Seventh, most chapters end with a **Summary Table** that lists the most important drugs and includes key information concerning their mechanisms of action, effects, clinical uses, pharmacokinetics, drug interactions, and toxicities.

Eighth, when preparing for a comprehensive examination, you should review the strategies described in **Appendix I** if you have not already done so. Then review the list of drugs in **Appendix II: Key Words for Key Drugs**. Students are also advised to check this appendix as they work through the chapters so they can begin to identify drugs out of the context of a chapter that reviews a restricted set of drugs.

Ninth, after you have worked your way through most or all of the chapters and have a good grasp of the Key Drugs, you should take the comprehensive examinations, each of 100 questions, presented in **Appendices III and IV**. These examinations are followed by a list of answers, each with a short explanation or rationale underlying the correct choice and the numbers of the chapters in which more information can be found if needed. We recommend that you take an entire examination or a block of questions as if it were a real examination: commit to answers for the whole set before you check the answers. As you work through the answers, make sure that you understand why each answer is either correct or incorrect. If you need to, return to the relevant chapters(s) to review the text that covers key concepts and facts that form the basis for the question.

We recommend that this book be used with a regular text. *Basic & Clinical Pharmacology*, 13th edition (McGraw-Hill, 2015), follows the chapter sequence used here. However, this review book is designed to complement any standard medical pharmacology text. The student who completes and understands *Pharmacology: Examination & Board Review* will greatly improve his or her performance and will have an excellent command of pharmacology.

Because it was developed in parallel with the textbook *Basic & Clinical Pharmacology*, this review book represents the authors' interpretations of chapters written by contributors to that text. We are grateful to those contributors, to our other

faculty colleagues, and to our students, who have taught us most of what we know about teaching.

We very much appreciate the invaluable contributions to this text afforded by the editorial team of Karen Edmonson, Rachel D'Annucci Henriquez, Shruti Awasthi, Harriet Lebowitz, and Michael Weitz. The authors also thank Katharine Katzung for her excellent proofreading contributions to this edition.

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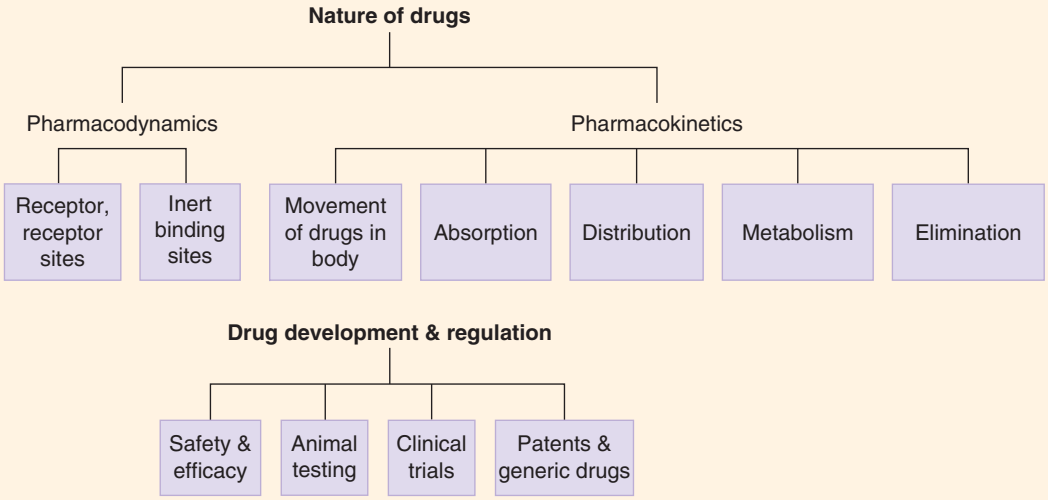
PART I BASIC PRINCIPLES

CHAPTER 1

Introduction

Pharmacology is the body of knowledge concerned with the action of chemicals on biologic systems. **Medical pharmacology** is the area of pharmacology concerned with the use of chemicals in the prevention, diagnosis, and treatment of disease, especially in humans. **Toxicology** is the area of pharmacology concerned with the undesirable effects of chemicals on biologic systems. **Pharmacokinetics** describes the effects of the body on drugs, eg, absorption, excretion, etc. **Pharmacodynamics** denotes the actions of the drug on the body, such as mechanism of action and therapeutic and toxic effects. The first part of this chapter reviews the basic principles of pharmacokinetics and pharmacodynamics that will be applied in subsequent chapters. The second part of the chapter reviews the development and regulation of drugs.



I. THE NATURE OF DRUGS

Drugs in common use include inorganic ions, nonpeptide organic molecules, small peptides and proteins, nucleic acids, lipids, and carbohydrates. Some are found in plants or animals, and others are partially or completely synthetic. Many drugs found in nature are **alkaloids,** which are molecules that have a basic pH in solution, usually as a result of amine groups in their structure. Many biologically important endogenous molecules and exogenous drugs are optically active; that is, they contain one or more asymmetric centers and can exist as enantiomers. The enantiomers of optically active drugs usually differ, sometimes more than 1000-fold, in their affinity for biologic receptor sites. Furthermore, such enantiomers may be metabolized at different rates in the body, with important clinical consequences.

A. Size and Molecular Weight

Drugs vary in size from molecular weight (MW) 7 (lithium) to over MW 50,000 (thrombolytic enzymes, antibodies, other proteins). Most drugs, however, have MWs between 100 and 1000. Drugs smaller than MW 100 are rarely sufficiently selective in their actions, whereas drugs much larger than MW 1000 are often poorly absorbed and poorly distributed in the body. Most protein drugs ("**biologicals**") are commercially produced in cell, bacteria, or yeast cultures using recombinant DNA technology.

B. Drug-Receptor Bonds

Drugs bind to receptors with a variety of chemical bonds. These include very strong covalent bonds (which usually result in irreversible action), somewhat weaker electrostatic bonds (eg, between a cation and an anion), and much weaker interactions (eg, hydrogen, van der Waals, and hydrophobic bonds).

PHARMACODYNAMIC PRINCIPLES

A. Receptors

Drug actions are mediated through the effects of drug ligand molecules on drug **receptors** in the body. Most receptors are large regulatory molecules that influence important biochemical processes (eg, enzymes involved in glucose metabolism) or physiologic processes (eg, ion channel receptors, neurotransmitter reuptake transporters, and ion transporters).

If drug-receptor binding results in activation of the receptor, the drug is termed an **agonist**; if inhibition results, the drug is considered an **antagonist**. Some drugs mimic *agonist* molecules by *inhibiting* metabolic enzymes, eg, acetylcholinesterase inhibitors. As suggested in Figure 1–1, a receptor molecule may have several binding sites. Quantitation of the effects of drug-receptor binding as a function of dose yields **dose-response curves** that provide information about the nature of the drug-receptor interaction. Dose-response phenomena are discussed in more detail in Chapter 2. A few drugs are enzymes themselves (eg, thrombolytic enzymes, pancreatic enzymes). These drugs do not act on endogenous receptors but on substrate molecules.

B. Receptor and Inert Binding Sites

Because most ligand molecules are much smaller than their receptor molecules (discussed in the text that follows), specific regions of receptor molecules provide the local areas responsible for drug binding. Such areas are termed **receptor sites** or **recognition sites**. In addition, drugs bind to some nonregulatory molecules in the body without producing a discernible effect. Such binding sites are termed **inert binding sites**. In some compartments of the

High-Yield Terms to Learn

Drugs	Substances that act on biologic systems at the chemical (molecular) level and alter their functions
Drug receptors	The molecular components of the body with which drugs interact to bring about their effects
Distribution phase	The phase of drug movement from the site of administration into the tissues
Elimination phase	The phase of drug inactivation or removal from the body by metabolism or excretion
Endocytosis, exocytosis	Endocytosis: Absorption of material across a cell membrane by enclosing it in cell membrane material and pulling it into the cell, where it can be processed or released. Exocytosis: Expulsion of material from vesicles in the cell into the extracellular space
Permeation	Movement of a molecule (eg, drug) through the biologic medium
Pharmacodynamics	The actions of a drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic actions
Pharmacokinetics	The actions of the body on the drug, including absorption, distribution, metabolism, and elimination. Elimination of a drug may be achieved by metabolism or by excretion. *Biodisposition* is a term sometimes used to describe the processes of metabolism and excretion
Transporter	A specialized molecule, usually a protein, that carries a drug, transmitter, or other molecule across a membrane in which it is not permeable, eg, Na^+/K^+ ATPase, serotonin reuptake transporter, etc
Mutagenic	An effect on the inheritable characteristics of a cell or organism—a mutation in the DNA; usually tested in microorganisms with the Ames test
Carcinogenic	An effect of inducing malignant characteristics
Teratogenic	An effect on the in utero development of an organism resulting in abnormal structure or function; not generally heritable

High-Yield Terms to Learn (*continued*)

Placebo	An inactive "dummy" medication made up to resemble the active investigational formulation as much as possible but lacking therapeutic effect
Single-blind study	A clinical trial in which the investigators—but not the subjects—know which subjects are receiving active drug and which are receiving placebos
Double-blind study	A clinical trial in which neither the subjects nor the investigators know which subjects are receiving placebos; the code is held by a third party
IND	Investigational New Drug Exemption; an application for FDA approval to carry out new drug trials in humans; requires animal data
NDA	New Drug Application; seeks FDA approval to market a new drug for ordinary clinical use; requires data from clinical trials as well as preclinical (animal) data
Phases 1, 2, and 3 of clinical trials	Three parts of a clinical trial that are usually carried out before submitting an NDA to the FDA
Positive control	A known standard therapy, to be used along with placebo, to evaluate the superiority or inferiority of a new drug in relation to the other drugs available
Orphan drugs	Drugs developed for diseases in which the expected number of patients is small. Some countries bestow certain commercial advantages on companies that develop drugs for uncommon diseases

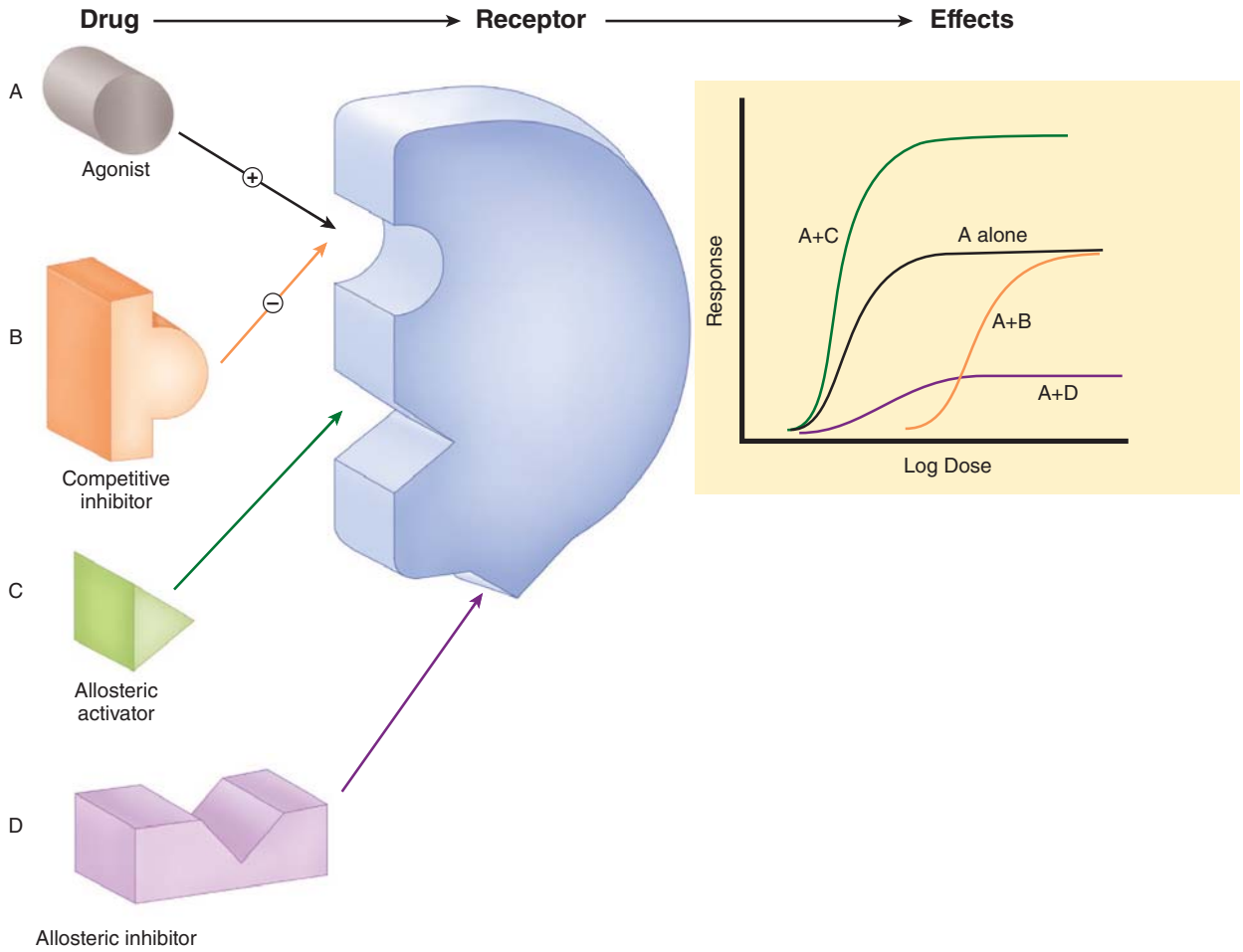


FIGURE 1–1 Potential mechanisms of drug interaction with a receptor. Possible effects resulting from these interactions are diagrammed in the dose-response curves at the right. The traditional agonist (drug A)-receptor binding process results in the dose-response curve denoted "A alone." B is a pharmacologic antagonist drug that competes with the agonist for binding to the receptor site. The dose-response curve produced by increasing doses of A in the presence of a fixed concentration of B is indicated by the curve "A+B." Drugs C and D act at different sites on the receptor molecule; they are *allosteric* activators or inhibitors. Note that allosteric inhibitors do not compete with the agonist drug for binding to the receptor, and they may bind reversibly or irreversibly. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology,* 12th ed. McGraw-Hill, 2012: Fig. 1–3.)

body (eg, the plasma), inert binding sites play an important role in buffering the concentration of a drug because bound drug does not contribute directly to the concentration gradient that drives diffusion. **Albumin** and **orosomucoid** (α_1-acid glycoprotein) are two important plasma proteins with significant drug-binding capacity.

PHARMACOKINETIC PRINCIPLES

To produce useful therapeutic effects, most drugs must be absorbed, distributed, and eliminated. Pharmacokinetic principles make rational dosing possible by quantifying these processes.

The Movement of Drugs in the Body

To reach its receptors and bring about a biologic effect, a drug molecule (eg, a benzodiazepine sedative) must travel from the site of administration (eg, the gastrointestinal tract) to the site of action (eg, the brain).

A. Permeation

Permeation is the movement of drug molecules into and within the biologic environment. It involves several processes, the most important of which are discussed next.

***1. Aqueous diffusion*—**Aqueous diffusion is the movement of molecules through the watery extracellular and intracellular spaces. The membranes of most capillaries have small water-filled pores that permit the aqueous diffusion of molecules up to the size of small proteins between the blood and the extravascular space. This is a passive process governed by Fick's law (see later discussion). The capillaries in the brain, testes, and some other organs lack aqueous pores, and these tissues are less exposed to some drugs.

***2. Lipid diffusion*—**Lipid diffusion is the passive movement of molecules through membranes and other lipid barriers. Like aqueous diffusion, this process is governed by Fick's law.

***3. Transport by special carriers*—**Drugs that do not readily diffuse through membranes may be transported across barriers by mechanisms that carry similar endogenous substances. A very large number of such transporter molecules have been identified, and many of these are important in the movement of drugs or as targets of drug action. Unlike aqueous and lipid diffusion, carrier transport is not governed by Fick's law and is capacity-limited. Important examples are transporters for ions (eg, Na^+/K^+ ATPase), for neurotransmitters (eg, transporters for serotonin, norepinephrine), for metabolites (eg, glucose, amino acids), and for foreign molecules **(xenobiotics)** such as anticancer drugs.

After release, amine neurotransmitters (dopamine, norepinephrine, and serotonin) and some other transmitters are recycled into nerve endings by transport molecules. Selective inhibitors for these transporters often have clinical value; for example, several antidepressants act by inhibiting the transport of amine neurotransmitters back into the nerve endings from which they have been released.

***4. Endocytosis*—**Endocytosis occurs through binding of the transported molecule to specialized components (receptors) on cell membranes, with subsequent internalization by infolding of that area of the membrane. The contents of the resulting intracellular vesicle are subsequently released into the cytoplasm of the cell. Endocytosis permits very large or very lipid-insoluble chemicals to enter cells. For example, large molecules such as proteins may cross cell membranes by endocytosis. Smaller, polar substances such as vitamin B_{12} and iron combine with special proteins (B_{12} with intrinsic factor and iron with transferrin), and the complexes enter cells by this mechanism. Because the substance to be transported must combine with a membrane receptor, endocytotic transport can be quite selective. **Exocytosis** is the reverse process, that is, the expulsion of material that is membrane-encapsulated inside the cell from the cell. Most neurotransmitters are released by exocytosis.

B. Fick's Law of Diffusion

Fick's law predicts the rate of movement of molecules across a barrier. The concentration gradient ($C_1 - C_2$) and permeability coefficient for the drug and the area and thickness of the barrier membrane are used to compute the rate as follows:

$$\text{Rate} = C_1 - C_2 \times \frac{\text{Permeability coefficient}}{\text{Thickness}} \times \text{Area} \qquad (1)$$

Thus, drug absorption is faster from organs with large surface areas, such as the small intestine, than from organs with smaller absorbing areas (the stomach). Furthermore, drug absorption is faster from organs with thin membrane barriers (eg, the lung) than from those with thick barriers (eg, the skin).

C. Water and Lipid Solubility of Drugs

***1. Solubility*—**The aqueous solubility of a drug is often a function of the electrostatic charge (degree of ionization, polarity) of the molecule, because water molecules behave as dipoles and are attracted to charged drug molecules, forming an aqueous shell around them. Conversely, the lipid solubility of a molecule is inversely proportional to its charge.

Many drugs are weak bases or weak acids. For such molecules, the *pH of the medium* determines the fraction of molecules charged (ionized) versus uncharged (nonionized). If the pK_a of the drug and the pH of the medium are known, the fraction of molecules in the ionized state can be predicted by means of the **Henderson-Hasselbalch** equation:

$$\log\left(\frac{\text{Protonated form}}{\text{Unprotonated form}}\right) = pK_a - pH \qquad (2)$$

"Protonated" means *associated with a proton* (a hydrogen ion); this form of the equation applies to both acids and bases.

***2. Ionization of weak acids and bases*—**Weak bases are ionized—and therefore more polar and more water-soluble—when they are protonated. Weak acids are not ionized—and so are less water-soluble—when they are protonated.

The following equations summarize these points:

$$\underset{\text{protonated weak base (charged, more water-soluble)}}{RNH_3^+} \rightleftharpoons \underset{\text{Unprotonated weak base (uncharged, more lipid-soluble)}}{RNH_2} + \underset{\text{proton}}{H^+} \quad (3)$$

$$\underset{\text{protonated weak acid (uncharged, more lipid-soluble)}}{RCOOH} \rightleftharpoons \underset{\text{Unprotonated weak acid (charged, more water-soluble)}}{RCOO^-} + \underset{\text{proton}}{H^+} \quad (4)$$

The Henderson-Hasselbalch relationship is clinically important when it is necessary to estimate or alter the partition of drugs between compartments of differing pH. For example, most drugs are freely filtered at the glomerulus, but lipid-soluble drugs can be rapidly reabsorbed from the tubular urine. If a patient takes an overdose of a weak acid drug, for example, aspirin, the excretion of this drug is faster in alkaline urine. This is because a drug that is a weak acid dissociates to its charged, polar form in alkaline solution, and this form cannot readily diffuse from the renal tubule back into the blood; that is, the drug is trapped in the tubule. Conversely, excretion of a weak base (eg, pyrimethamine, amphetamine) is faster in acidic urine (Figure 1–2).

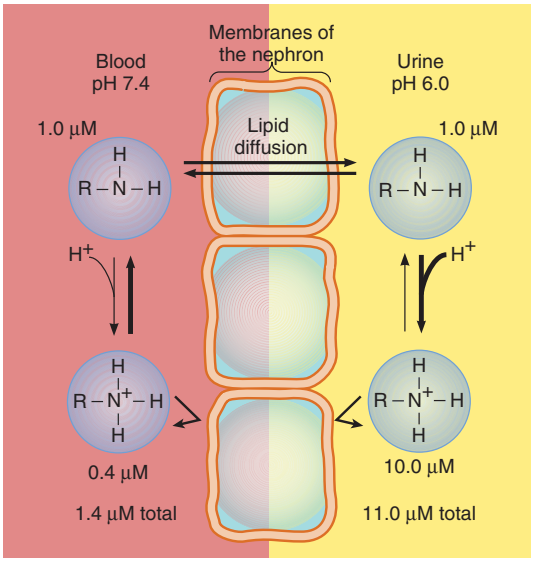


FIGURE 1–2 The Henderson-Hasselbalch principle applied to drug excretion in the urine. Because the nonionized form diffuses readily across the lipid barriers of the nephron, this form may reach equal concentrations in the blood and urine; in contrast, the ionized form does not diffuse as readily. Protonation occurs within the blood and the urine according to the Henderson-Hasselbalch equation. Pyrimethamine, a weak base of pK_a 7.0, is used in this example. At blood pH, only 0.4 µmol of the protonated species will be present for each 1.0 µmol of the unprotonated form. The total concentration in the blood will thus be 1.4 µmol/L if the concentration of the unprotonated form is 1.0 µmol/L. In the urine at pH 6.0, 10 µmol of the nondiffusible ionized form will be present for each 1.0 µmol of the unprotonated, diffusible form. Therefore, the total urine concentration (11 µmol/L) may be almost 8 times higher than the blood concentration.

Absorption of Drugs

A. Routes of Administration

Drugs usually enter the body at sites remote from the target tissue or organ and thus require transport by the circulation to the intended site of action. To enter the bloodstream, a drug must be absorbed from its site of administration (unless the drug has been injected directly into the vascular compartment). The rate and efficiency of absorption differ depending on a drug's route of administration. In fact, for some drugs, the amount absorbed may be only a small fraction of the dose administered when given by certain routes. The amount absorbed into the systemic circulation divided by the amount of drug administered constitutes its **bioavailability** by that route. Common routes of administration and some of their features are listed in Table 1–1.

TABLE 1–1 Common routes of drug administration.

Oral (swallowed)	Offers maximal convenience; absorption is often slower. Subject to the **first-pass effect**, in which a significant amount of the agent is metabolized in the gut wall, portal circulation, and liver before it reaches the systemic circulation
Buccal and sublingual (not swallowed)	Direct absorption into the systemic venous circulation, bypassing the hepatic portal circuit and first-pass metabolism
Intravenous	Instantaneous and complete absorption (by definition, bioavailability is 100%). Potentially more dangerous
Intramuscular	Often faster and more complete (higher bioavailability) than with oral administration. Large volumes may be given if the drug is not too irritating. First-pass metabolism is avoided
Subcutaneous	Slower absorption than the intramuscular route. First-pass metabolism is avoided.
Rectal (suppository)	The rectal route offers partial avoidance of the first-pass effect. Larger amounts of drug and drugs with unpleasant tastes are better administered rectally than by the buccal or sublingual routes
Inhalation	Route offers delivery closest to respiratory tissues (eg, for asthma). Usually very rapid absorption (eg, for anesthetic gases)
Topical	The topical route includes application to the skin or to the mucous membrane of the eye, ear, nose, throat, airway, or vagina for *local* effect
Transdermal	The transdermal route involves application to the skin for *systemic* effect. Absorption usually occurs very slowly (because of the thickness of the skin), but the first-pass effect is avoided