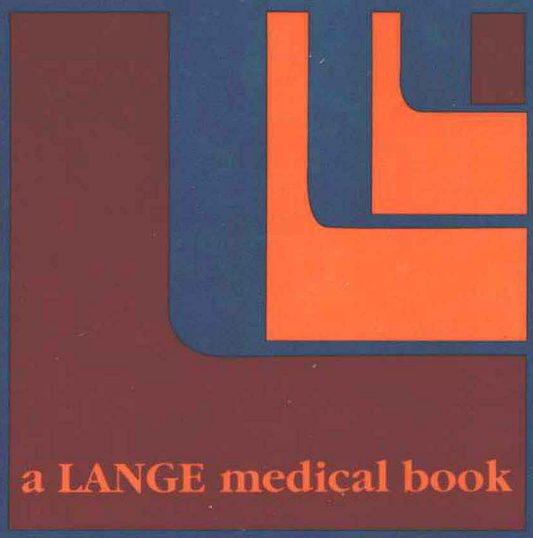
sixth
edition

Basic & Clinical Pharmacology

Bertram G. Katzung



a LANGE medical book

Basic & Clinical Pharmacology

sixth edition

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Preface

This book is designed to provide a complete, authoritative, current, and readable pharmacology text for medical, pharmacy, and other health science students. It also offers special features that make it useful to house officers and practicing clinicians.

Information is organized according to the sequence used in 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 builds new information on information already assimilated. For example, early presentation of autonomic pharmacology allows students to integrate the physiology and neuroscience they know with the pharmacology they are learning and prepares them to understand the autonomic effects of other drugs. This is especially important for the cardiovascular and CNS groups. However, chapters can be used equally well in courses that present these topics in a different sequence.

Within each chapter, emphasis is placed on drug groups and prototypes rather than repetitive detail about individual drugs. We are pleased to see that other pharmacology textbooks are now adopting this approach. The selection and order of presentation of material are based on the accumulated experience of teaching this material to several thousand medical, pharmacy, dental, podiatry, nursing, and other health science students.

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; *clinical pharmacology* is an integral part of this text. In addition, lists of the preparations available, including trade and generic names and dosage formulations, are provided at the end of each chapter for easy reference by the house officer or practitioner who is writing a chart order or prescription.

Because of the explosive increase in the number of recognized receptors, receptor nomenclature is unstable at present. In order to minimize discrepancies, we have chosen to use the receptor names given in the 1993 and 1994 issues of *Receptor Nomenclature Supplement* (special annual issues of *Trends in Pharmacological Sciences*) in most cases. Enzymes are named according to the contributor's judgment of the best current usage, usually that of *1992 Enzyme Nomenclature,* Academic Press, 1992.

Significant revisions in this edition include the following:

- Many new figures, some in color, that help to clarify important concepts in pharmacology
- Special interest sections, set off as boxed text, that provide working examples of the text material or serve to point out items of special interest
- Substantial expansion of the coverage of general concepts relating to receptors, including their molecular biology, interactions with drugs, and effector mechanisms in Chapter 2 and other chapters
- Expanded coverage of the enteric nervous system and of newly described muscarinic, norepinephrine, histamine, and serotonin receptors in appropriate chapters
- New sections on the important new fluoroquinolone antibiotics, RU 486, neurotransmitters in the enteric nervous system, current understanding of the GABA receptor, and rational prescribing and prescribing errors
- Recent changes in the clinical management of asthma, congestive heart failure, hypertension, and Alzheimer's disease
- Descriptions of important new drugs released through May 1994
- Revised bibliographies with many new references through 1993

ADDITIONAL SOURCES OF INFORMATION

Pharmacology: Examination & Board Review (Appleton & Lange) provides a succinct review of pharmacology with one of the largest available collections of sample examination questions and answers. It is especially helpful to students preparing for board-type examinations.

Drug Therapy, 2nd ed (Appleton & Lange, 1991), is a pocket-size reference to the properties, prescribing, and use of drugs on hospital wards and in outpatient practice. This clinical manual is designed for students in clinical training, house staff, and practicing physicians.

The widespread acceptance of the first five editions of *Basic & Clinical Pharmacology* over more than a decade suggests that this book fills an important need. We believe that the sixth edition will satisfy this need even more effectively. Spanish, Portuguese, Italian, and Indonesian translations are available. Translations into other languages are under way; the publisher may be contacted for additional information.

I wish to acknowledge the ongoing efforts of my contributing authors and the major contributions of the staff at Appleton & Lange and of our editor, James Ransom.

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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San Francisco
June 1994

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Section I.
Basic Principles

Introduction 1

Bertram G. Katzung, MD, PhD

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 that deals with the undesirable effects of chemicals on living systems, from individual cells to complex ecosystems.

History

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 painstaking 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, etc.

Around the end of the 17th century, reliance on observation and experimentation began to replace theorizing in medicine as well as in the physical sciences. As the value of these methods in the study of disease became clear, physicians in Great Britain and elsewhere in Europe began to apply them to the effects of traditional drugs used in their own practices. Thus, *pharmacotherapy,* the medical use of drugs, began to develop as the precursor to pharmacology. However, any understanding of the mechanisms of action of drugs was still prevented by the absence of methods for purifying active agents from the crude remedies that were available and—even more—by the lack of methods for testing hypotheses about the nature of drug actions. However, 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 and 19th centuries laid the foundation needed for understanding how drugs work at the organ and tissue levels. Paradoxically, real advances in basic pharmacology during the 19th century 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.

About 50 years ago, there also began a major expansion of research efforts in all areas of biology. As new concepts and new techniques were introduced, information accumulated about drug action and the biologic substrate of that action, the receptor. During this half-century, many fundamentally new drug groups and new members of old groups have been introduced. The last 3 decades have seen an even more rapid growth of information and understanding of the molecular basis for drug action. The molecular mechanisms of action of many drugs have now been identified, and numerous receptors have been isolated, structurally characterized, and cloned. Much of that progress is summarized in this book.

The extension of scientific principles into everyday therapeutics is still going on, though the consuming public, unfortunately, is still exposed to vast amounts of inaccurate, incomplete, or unscientific information regarding the pharmacologic effects of chemicals. This has resulted in the faddish use of innumerable expensive, ineffective, and sometimes harmful remedies and the growth of a huge "alternative health care" industry. Conversely, lack of understanding of basic scientific principles in biology and statistics and the absence of critical thinking about public health issues has led to rejection of medical science by a segment of the public and a tendency to assume that all adverse drug effects are the result of malpractice.

The Nature of Drugs

In the most general sense, a drug may be defined as any substance that brings about a change in biologic function through its chemical actions. In the great majority of cases, the drug molecule interacts with a specific molecule in the biologic system that plays, as noted above, a regulatory role, ie, a **receptor** molecule. The nature of receptors is discussed more fully in Chapter 2. In a very small number of cases, drugs known as chemical antagonists may interact directly with other drugs, while a few drugs (eg, osmotic agents) interact almost exclusively with water molecules. Drugs may be synthesized within the body (eg, hormones) or may be chemicals *not* synthesized in the body, ie, xenobiotics (from Gr *xenos* "stranger"). Poisons are drugs. Toxins are usually defined as poisons of biologic origin, ie, synthesized by plants or animals, in contrast to inorganic poisons such as lead and arsenic.

In order to interact chemically with its receptor, a drug molecule must have the appropriate size, electrical charge, shape, and atomic composition. Furthermore, a drug is often administered at a location distant from its intended site of action, eg, a pill given orally to relieve a headache. Therefore, a useful drug must have the necessary properties to be transported from its site of administration to its site of action. Finally, a practical drug should be inactivated or excreted from the body at a reasonable rate so that its actions will be of appropriate duration.

A. The Physical Nature of Drugs: Drugs may be solid at room temperature (eg, aspirin, atropine), liquid (eg, nicotine, ethanol), or gaseous (eg, nitrous oxide). These factors often determine the best route of administration. For example, some liquid drugs are easily vaporized and can be inhaled in that form, eg, halothane, amyl nitrite. The common routes of administration are discussed in Chapter 3. The various classes of organic compounds—carbohydrates, proteins, lipids, and their constituents—are all represented in pharmacology. Many drugs are weak acids or bases. This fact has important implications for the way they are handled by the body, because pH differences in the various compartments of the body may alter the degree of ionization of such drugs (see below).

B. Drug Size: The molecular size of drugs in current use varies from very small (lithium ion, MW 7) to very large (eg, alteplase [t-PA], a protein of MW 59,050). However, the vast majority of drugs have molecular weights between 100 and 1000. The lower limit of this narrow range is probably set by the requirements for specificity of action. In order to have a good "fit" to only one type of receptor, a drug molecule must be sufficiently unique in shape, charge, etc, to prevent its binding to other receptors. To achieve such selective binding, it appears that a molecule should in most cases be at least 100 MW units in size. The upper limit in molecular weight is determined primarily by the requirement that drugs be able to move within the body (eg, from site of administration to site of action). Drugs much larger than MW 1000 will not diffuse readily between compartments of the body (see Permeation, below). Therefore, very large drugs (usually proteins) must be administered directly into the compartment where they have their effect. In the case of alteplase, a clot-dissolving enzyme, the drug is administered directly into the vascular compartment by intravenous infusion.

C. Drug Reactivity and Drug-Receptor Bonds: Drugs interact with receptors by means of chemical forces or bonds. These are of three major types: covalent, electrostatic, and hydrophobic. Covalent bonds are very strong and in many cases not reversible under biologic conditions. Thus, the covalent bond formed between the activated form of phenoxybenzamine and the alpha receptor for norepinephrine (which results in blockade of the receptor) is not readily broken. The blocking effect of phenoxybenzamine lasts long after the free drug has disappeared from the bloodstream and is reversed only by the synthesis of new alpha receptors, a process that takes about 48 hours. Other examples of highly reactive, covalent bond-forming drugs are the DNA-alkylating agents used in cancer chemotherapy to disrupt cell division in the neoplastic tissue.

Electrostatic bonding is much more common than covalent bonding in drug-receptor interactions. Electrostatic bonds vary from relatively strong linkages between permanently charged ionic molecules to weaker hydrogen bonds and very weak induced dipole interactions such as van der Waals forces and similar phenomena. Electrostatic bonds are weaker than covalent bonds.

Hydrophobic bonds are usually quite weak and are probably important in the interactions of highly lipid-soluble drugs with the lipids of cell membranes and perhaps in the interaction of drugs with the internal walls of receptor "pockets."

The specific nature of a particular drug-receptor bond is of less practical importance than the fact that drugs which bind through weak bonds to their recep-

tors are generally more selective than drugs which bind through very strong bonds. This is because weak bonds require a very precise fit of the drug to its receptor if an interaction is to occur. Only a few receptor types are likely to provide such a precise fit for a particular drug structure. Thus, if we wished to design a highly selective short-acting drug for a particular receptor, we would avoid highly reactive molecules that form covalent bonds and instead choose molecules that form weaker bonds.

A few substances that are almost completely inert in the chemical sense nevertheless have significant pharmacologic effects. For example, xenon, an "inert gas," has anesthetic effects at elevated pressures.

D. Drug Shape: The shape of a drug molecule must be such as to permit binding to its receptor site. Optimally, the drug's shape is complementary to that of the receptor site in the same way that a key is complementary to a lock. Furthermore, the phenomenon of **chirality** (stereoisomerism) is so common in biology that more than half of all useful drugs are chiral molecules, ie, they exist as enantiomeric pairs. Drugs with two asymmetric centers have four diastereomers, eg, labetalol, an alpha- and beta-receptor-blocking drug. In the great majority of cases, one of these enantiomers will be much more effective than its mirror image enantiomer, reflecting a better fit to the receptor molecule. For example, the *S*(+) enantiomer of methacholine, a parasympathomimetic drug, is over 250 times more potent than the *R*(−) enantiomer. If one imagines the receptor site to be like a glove into which the drug molecule must fit to bring about its effect, it is clear why a "left-oriented" drug will be more effective in binding to a left-hand receptor than will its "right-oriented" enantiomer.

The more active enantiomer at one type of receptor site may not be more active at another type, eg, a receptor type that may be responsible for some unwanted effect. For example, carvedilol, a drug that interacts with adrenoceptors, has a single chiral center and thus two enantiomers (Table 1–1). One of these enantiomers, the *S*(−) isomer, is a potent beta receptor blocker. The *R*(+) isomer is 100-fold weaker at the beta receptor. However, the isomers are approximately equipotent as alpha receptor blockers. Ketamine is an intravenous anesthetic. The (+) enantiomer is a more potent anesthetic and is less toxic than the (−) enantiomer. Unfortunately, the drug is still used as the racemic mixture.

Finally, because enzymes are usually stereoselective, one drug enantiomer is often more susceptible than the other to drug-metabolizing enzymes. As a result, the duration of action of one enantiomer may be quite different from that of the other.

Unfortunately, most studies of clinical efficacy and drug elimination in humans have been carried out with racemic mixtures of drugs rather than with the separate enantiomers. At present, only about 45% of the chiral drugs used clinically are marketed as the active isomer—the rest are available only as racemic mixtures. As a result, many patients are receiving drug doses of which 50% or more is either inactive or actively toxic. However, there is increasing interest—at both the scientific and the regulatory levels—in making more chiral drugs available as their active enantiomers.

E. Rational Drug Design: Rational design of drugs implies the ability to predict the appropriate molecular structure of a drug on the basis of information about its biologic receptor. Until recently, no receptor was known in sufficient detail to permit such drug design. Instead, drugs were developed through random testing of chemicals or modification of drugs already known to have some effect (Chapter 5). However, during the past 2 decades, many receptors have been isolated and characterized. A few drugs now in use were developed through molecular design based on a knowledge of the three-dimensional structure of the receptor site. Computer programs are now available that can iteratively optimize drug structures to fit known receptors. As more becomes known about receptor structure, rational drug design will become more feasible.

Table 1–1. Dissociation constants (K_d) of the enantiomers and racemate of carvedilol. The K_d is the concentration for 50% saturation of the receptors and is inversely proportionate to the affinity of the drug for the receptors.[1]

Form of Carvedilol	Inverse of Affinity for Alpha Receptors (K_d, nmol/L)	Inverse of Affinity for Beta Receptors (K_d, nmol/L)
R(+) enantiomer	14	45
S(−) enantiomer	16	0.4
R,S(+/−)	11	0.9

[1]Data from Ruffolo RR et al: The pharmacology of carvedilol. Eur J Pharmacol 1990;38:S82.

Drug-Body Interactions

The interactions between a drug and the body are conveniently divided into two classes. The actions of the drug on the body are termed **pharmacodynamic** processes and are presented in greater detail in Chapter 2. These properties determine the group in which the drug is classified and often play the major role in deciding whether that group is appropriate therapy for a particular symptom or disease. The actions of the body on the drug are called **pharmacokinetic** processes and are described in Chapters 3 and 4. Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient, eg, one with impaired renal function. The following paragraphs provide a brief introduction to pharmacodynamics and pharmacokinetics.

Pharmacodynamic Principles

As noted above, most drugs must bind to a receptor to bring about an effect. However, at the molecular level, drug binding is only the first in what is often a complex sequence of steps.

A. Types of Drug-Receptor Interactions: **Agonist** drugs bind to and *activate* the receptor in some fashion, which directly or indirectly brings about the effect. Some receptors incorporate effector machinery in the same molecule, so that drug binding brings about the effect directly, eg, opening of an ion channel or activation of enzyme activity. Other receptors are linked through one or more intervening **coupling molecules** to a separate **effector molecule.** The several types of drug-receptor-effector coupling systems are discussed in Chapter 2. Pharmacologic **antagonist** drugs, by binding to a receptor, *prevent* binding by other molecules. For example, acetylcholine receptor blockers such as atropine are antagonists because they prevent access of acetylcholine and similar agonist drugs to the acetylcholine receptor. These agents reduce the effects of acetylcholine and similar drugs in the body. In contrast, drugs that prevent the binding of acetylcholine to acetylcholinesterase (cholinesterase inhibitors) slow down the normal termination of action of acetylcholine released in the body and greatly increase the action of this neurotransmitter. Thus, cholinesterase inhibitors have actions in the patient that resemble those of acetylcholine receptor agonists.

B. Duration of Drug Action: Termination of drug action at the receptor level results from one of several processes. In some cases, the effect lasts only as long as the drug occupies the receptor, so that dissociation of drug from the receptor automatically terminates the effect. In many cases, however, the action may persist after the drug has dissociated, because, for example, some coupling molecule is still present in activated form. In the case of drugs that bind covalently to the receptor, the effect may persist until the drug-receptor complex is destroyed and new receptors are synthesized, as described previously for phenoxybenzamine. Finally, some receptor-effector systems incorporate **desensitization** mechanisms for preventing excessive activation when drug molecules continue to be present for long periods. See Chapter 2 for additional details.

C. Receptors and Inert Binding Sites: To function as a receptor, an endogenous molecule must first be selective in choosing ligands (drug molecules) to bind; and second, it must change its function upon binding in such a way that the function of the biologic system (cell, tissue, etc) is altered. The first characteristic is required to avoid constant activation of the receptor by promiscuous binding of large numbers of ligands. The second characteristic is clearly necessary if the ligand is to cause a pharmacologic effect. The body contains many molecules that are capable of binding drugs, however, and not all of these endogenous molecules are regulatory molecules. Binding of a drug to a nonregulatory molecule such as plasma albumin will result in no detectable change in the function of the biologic system, so the endogenous molecule can be called an inert binding site. Such binding is not completely without significance, however, since it affects the distribution of drug within the body and will determine the amount of free drug in the circulation. Both of these factors are of pharmacokinetic importance (see below and Chapter 3).

Pharmacokinetic Principles

In practical therapeutics, a drug should be able to reach its intended site of action after administration by some convenient route. In only a few situations is it possible to directly apply a drug to its target tissue, eg, by topical application of an anti-inflammatory agent to inflamed skin or mucous membrane. In other cases, drugs may be given intravenously and circulate in the blood directly to target blood vessels in another part of the body where they bring about useful effects. Much more commonly, a drug is given into one body compartment, eg, the gut, and must move to its site of action in another compartment, eg, the brain. This requires that the drug be **absorbed** into the blood from its site of administration and **distributed** to its site of action, **permeating** through the various barriers that separate these compartments. For a drug given orally to produce an effect in the central nervous system, these barriers include the tissues that comprise the wall of the intestine, the walls of the capillaries that perfuse the gut, and the "blood-brain barrier," the walls of the capillaries that perfuse the brain. Finally, after bringing about its effect, a drug should be **eliminated** at a reasonable rate by metabolic inactivation, by excretion from the body, or by a combination of these processes.

A. Permeation: Drug permeation proceeds by four primary mechanisms. Passive diffusion in an aqueous or lipid medium is most common, but active processes play a role in the movement of some drugs, especially those whose molecules are too large to diffuse readily.

1. Aqueous diffusion–Aqueous diffusion occurs within the larger aqueous compartments of the body (interstitial space, cytosol, etc) and across epithelial membrane tight junctions and the endothelial lining of blood vessels through aqueous pores that permit the passage of molecules as large as MW 20,000–30,000.* Aqueous diffusion of drug molecules is usually driven by the concentration gradient of the permeating drug, a downhill movement described by Fick's law (see below). Drug molecules

*The capillaries of the brain and the testes are characterized by an absence of the pores that permit aqueous diffusion of many drug molecules into the tissue. These tissues are therefore "protected" or "sanctuary" sites from many circulating drugs.

that are bound to large plasma proteins (eg, albumin) will not permeate these aqueous pores. If the drug is charged, its flux is also influenced by electrical fields (eg, the membrane potential and—in parts of the nephron—the transtubular potential).

2. Lipid diffusion–Lipid diffusion is the most important limiting factor for drug permeation because of the large number of lipid barriers that separate the compartments of the body. Because these lipid barriers separate aqueous compartments, the lipid:aqueous partition coefficient of a drug determines how readily the molecule moves between aqueous and lipid media. In the case of weak acids and weak bases (which gain or lose electrical charge-bearing protons, depending on the pH), the ability to move from aqueous to lipid or vice versa varies with the pH of the medium, because charged molecules attract water molecules. The ratio of lipid-soluble form to aqueous-soluble form for a weak acid or weak base is expressed by the Henderson-Hasselbalch equation (see below).

3. Special carriers–Special carrier molecules exist for certain substances that are important for cell function and too large or too insoluble in lipid to diffuse passively through membranes, eg, peptides, amino acids, glucose. These carriers bring about movement by active transport or facilitated diffusion and, unlike passive diffusion, are saturable and inhibitable. Because many drugs are or resemble such naturally occurring peptides, amino acids, or sugars, they can use these carriers to cross membranes.

4. Endocytosis and exocytosis–A few substances are so large that they can enter cells only by endocytosis, the process by which the substance is engulfed by the cell membrane and carried into the cell by pinching off of the newly formed vesicle inside the membrane. The substance can then be released inside the cytosol by breakdown of the vesicle membrane. This process is responsible for the transport of iron and vitamin B_{12}, each complexed with appropriate binding proteins, across the wall of the gut into the blood. The reverse process (exocytosis) is responsible for the secretion of many substances from cells. For example, many neurotransmitter substances are stored in membrane-bound vesicles in nerve endings to protect them from metabolic destruction in the cytoplasm. Appropriate activation of the nerve ending causes fusion of the storage vesicle with the cell membrane and expulsion of its contents into the extracellular space.

B. Fick's Law of Diffusion: The passive flux of molecules down a concentration gradient is given by Fick's law:

$$\text{Flux (molecules per unit time)} = (C_1 - C_2) \times \frac{\text{Area} \times \text{Permeability coefficient}}{\text{Thickness}}$$

where C_1 is the higher concentration, C_2 is the lower concentration, area is the area across which diffusion is occurring, permeability coefficient is a measure of the mobility of the drug molecules in the medium of the diffusion path, and thickness is the thickness (length) of the diffusion path. In the case of lipid diffusion, the lipid:aqueous partition coefficient is a major determinant of mobility of the drug, since it determines how readily the drug enters the lipid membrane from the aqueous medium.

C. Ionization of Weak Acids and Weak Bases: The electrostatic charge of an ionized molecule attracts water dipoles and results in a polar, relatively water-soluble and lipid-insoluble complex. Since lipid diffusion depends on relatively high lipid solubility, ionization of drugs may markedly reduce their ability to permeate membranes. A very large fraction of the drugs in use are weak acids or weak bases (Table 1–2). For drugs, a weak acid is best defined as a neutral molecule that can reversibly dissociate into an anion (a negatively charged molecule) and a proton (a hydrogen ion). For example, aspirin dissociates as follows:

$$\underset{\text{Neutral aspirin}}{C_8H_7O_2COOH} \rightleftharpoons \underset{\text{Aspirin anion}}{C_8H_7O_2COO^-} + \underset{\text{Proton}}{H^+}$$

A drug that is a weak base can be defined as a neutral molecule that can form a cation (a positively charged molecule) by combining with a proton. For example, pyrimethamine, an antimalarial drug, undergoes the following association-dissociation process:

$$\underset{\text{Pyrimethamine cation}}{C_{12}H_{11}ClN_3NH_3^+} \rightleftharpoons \underset{\text{Neutral pyrimethamine}}{C_{12}H_{11}ClN_3NH_2} + \underset{\text{Proton}}{H^+}$$

Note that the protonated form of a weak acid is the neutral, more lipid-soluble form, whereas the unprotonated form of a weak base is the neutral form. The law of mass action requires that these reactions move to the left in an acid environment (low pH, excess protons available) and to the right in a basic environment. The Henderson-Hasselbalch equation relates the ratio of protonated to unprotonated weak acid or weak base to the molecule's pK_a and the pH of the medium as follows:

$$\log \frac{\text{(Protonated)}}{\text{(Unprotonated)}} = pK_a - pH$$

This equation applies to both acidic and basic drugs. Inspection confirms that the lower the pH relative to the pK_a, the greater will be the fraction of drug in the protonated form. Because the uncharged form