KATZUNG & TREVOR's
Pharmacology
EXAMINATION & BOARD REVIEW

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Katzung & Trevor's

Pharmacology
Examination
& Board Review

Twelfth Edition

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Notice

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Contents

Preface

This book is designed to help students review pharmacology and to prepare for both regular course examinations and board examinations. The twelfth 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*, 14th 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*, 14th edition (McGraw-Hill, 2018), 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 Peter Boyle and Michael Weitz. The authors also thank Katharine Katzung for her excellent copyediting and proofreading contributions to this edition.

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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, metabolism, 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 discovery and development of new drugs and the regulation of drugs.

Nature of drugs

Pharmacodynamics

- Receptor, receptor sites
- Inert binding sites

Pharmacokinetics

- Movement of drugs in body
- Absorption
- Distribution
- Metabolism
- Elimination

Drug development & regulation

- Safety & efficacy
- Animal testing
- Clinical trials
- Patents & generic drugs
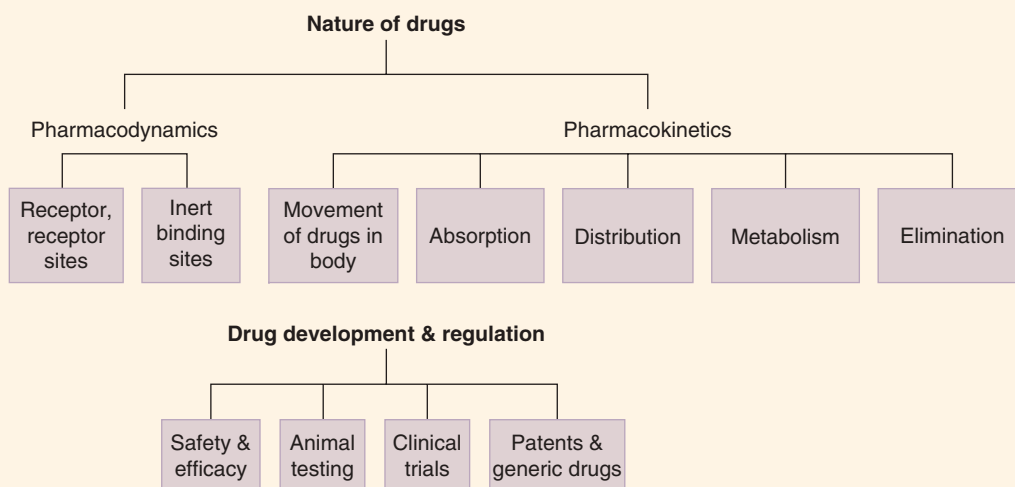
■ I. THE NATURE OF DRUGS

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 (alkaline) 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 reversible 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 molecule, 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 interaction as a function of dose (or concentration) 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

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; **adaptive** trials, combined two or more phases
Positive control	A known standard therapy, to be used in addition to 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
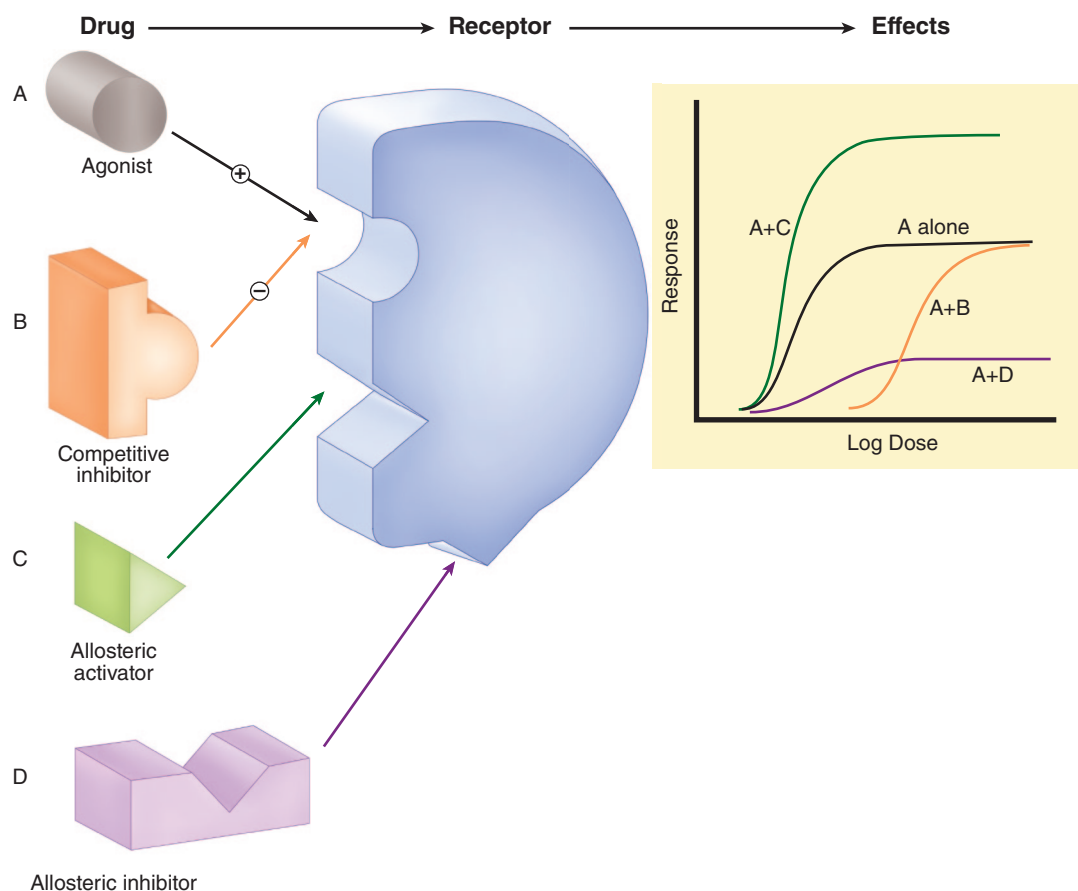
FIGURE 1–1 Potential mechanisms of drug interaction with a receptor. Possible effects resulting from these interactions are diagrammed in the dose-response curves at the right. The traditional agonist (drug A)-receptor binding process results in the dose-response curve denoted "A alone." B is a pharmacologic 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.)

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 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 2 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 include the following:

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 lipid bilayer cell 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 has a maximum capacity, ie, is saturable. 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 selective 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 or into nearby cells.

4. Endocytosis—Endocytosis occurs through binding of the 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 out of 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:

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

Thus, drug absorption into the blood is faster within 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:

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

"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:

$$RNH_3^+ \rightleftharpoons RNH_2 + H^+ \quad (3)$$

protonated weak base (charged, more water-soluble)   Unprotonated weak base (uncharged, more lipid-soluble)   proton

$$RCOOH \rightleftharpoons RCOO^- + H^+ \quad (4)$$

protonated weak acid (uncharged, more lipid-soluble)   Unprotonated weak acid (charged, more water-soluble)   proton
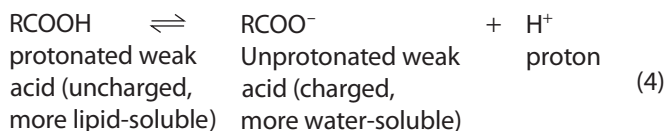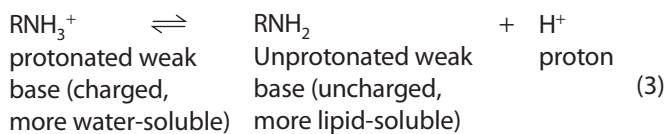
The Henderson-Hasselbalch relationship is clinically important when it is necessary to estimate or alter the partition of drugs between compartments of differing pH. For example, most drugs are freely filtered at the glomerulus, but lipid-soluble drugs can be rapidly reabsorbed from the tubular urine. 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).

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 as well as the drug's physicochemical properties. 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.

B. Blood Flow

Blood flow influences absorption from intramuscular and subcutaneous sites and, in shock, from the gastrointestinal tract as well. High blood flow maintains a high concentration gradient between the drug depot and the blood and thus facilitates absorption.

C. Concentration

The concentration of drug at the site of administration is important in determining the concentration gradient relative to the blood as noted previously. As indicated by Fick's law (Equation 1), the
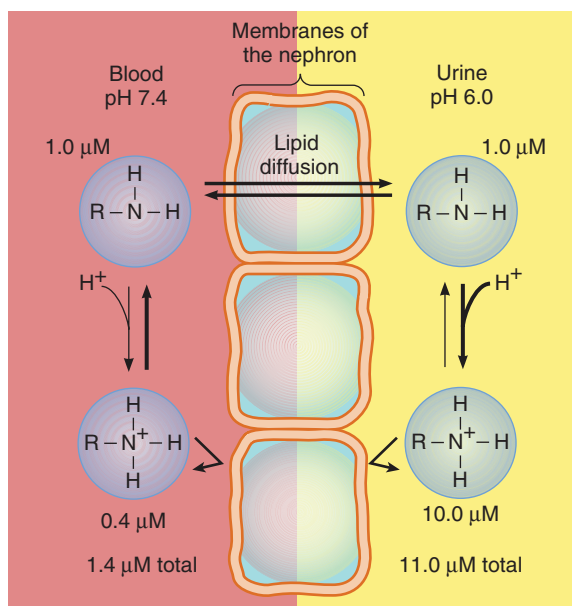
FIGURE 1–2 The Henderson-Hasselbalch principle applied to drug excretion in the urine. Because the nonionized, uncharged form diffuses readily across the lipid barriers of the nephron, this form may reach equal concentrations in the blood and urine; in contrast, the ionized form does not diffuse as readily. 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.

concentration gradient is a major determinant of the rate of absorption. Drug concentration in the vehicle is particularly important in the absorption of drugs applied topically.

Distribution of Drugs

A. Determinants of Distribution

1. Size of the organ—The size of the organ determines the concentration gradient between blood and the organ. For example, skeletal muscle can take up a large *amount* of drug because the *concentration* in the muscle tissue remains low (and the blood-tissue gradient high) even after relatively large amounts of drug have been transferred; this occurs because skeletal muscle is a very large organ. In contrast, because the brain is smaller, distribution of a smaller amount of drug into it will raise the tissue concentration and reduce to zero the blood-tissue concentration gradient, preventing further uptake of drug unless it is actively transported.

2. Blood flow—Blood flow to the tissue is an important determinant of the *rate of uptake* of drug, although blood flow may not affect the *amount* of drug in the tissue at equilibrium. As a result, well-perfused tissues (eg, brain, heart, kidneys, and splanchnic

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. **Bioavailability** may be limited by the first pass effect.
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 bio-availability) 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 taste 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 utilizes 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.

organs) usually achieve high tissue concentrations sooner than poorly perfused tissues (eg, fat, bone).

3. Solubility—The solubility of a drug in tissue influences the concentration of the drug in the extracellular fluid surrounding the blood vessels. If the drug is very soluble in the cells, the concentration in the perivascular extracellular space will be lower and diffusion from the vessel into the extravascular tissue space will be facilitated. For example, some organs (such as the brain) have a high lipid content and thus dissolve a high concentration of lipid-soluble agents rapidly.

4. Binding—Binding of a drug to macromolecules in the blood or a tissue compartment tends to increase the drug's concentration in that compartment. For example, warfarin is strongly bound to plasma albumin, which restricts warfarin's diffusion out of the vascular compartment. Conversely, chloroquine is strongly bound

TABLE 1–2 Average values for some physical volumes within the adult human body.

Compartment	Volume (L/kg body weight)
Plasma	0.04
Blood	0.08
Extracellular water	0.2
Total body water	0.6
Fat	0.2–0.35

to extravascular tissue proteins, which results in a marked reduction in the plasma concentration of chloroquine.

B. Apparent Volume of Distribution and Physical Volumes

The apparent volume of distribution (V_d) is an important pharmacokinetic parameter that reflects the above determinants of the distribution of a drug in the body. V_d relates the amount of drug in the body to the concentration in the plasma (Chapter 3). In contrast, the *physical* volumes of various body compartments are less important in pharmacokinetics (Table 1–2). However, obesity alters the ratios of total body water to body weight and fat to total body weight, and this may be important when using highly lipid-soluble drugs. A simple approximate rule for the aqueous compartments of the normal body is as follows: 40% of total body weight is intracellular water and 20% is extracellular water; thus, water constitutes approximately 60% of body weight.

Metabolism of Drugs

Drug **disposition** is a term sometimes used to refer to metabolism and elimination of drugs. Some authorities use disposition to denote distribution as well as metabolism and elimination. Metabolism of a drug sometimes terminates its action, but other effects of drug metabolism are also important. Some drugs when given orally are metabolized before they enter the systemic circulation. This first-pass metabolism was referred to in Table 1–1 as one cause of low bioavailability. Drug metabolism occurs primarily in the liver and is discussed in greater detail in Chapter 4.

A. Drug Metabolism as a Mechanism of Activation or Termination of Drug Action

The action of many drugs (eg, sympathomimetics, phenothiazines) is terminated before they are excreted because they are metabolized to biologically inactive derivatives. Conversion to an inactive metabolite is a form of **elimination**.

In contrast, **prodrugs** (eg, levodopa, minoxidil) are inactive as administered and must be metabolized in the body to become active. Many drugs are active as administered and have active metabolites as well (eg, morphine, some benzodiazepines).

B. Drug Elimination Without Metabolism

Some drugs (eg, lithium, many others) are not modified by the body; they continue to act until they are excreted.
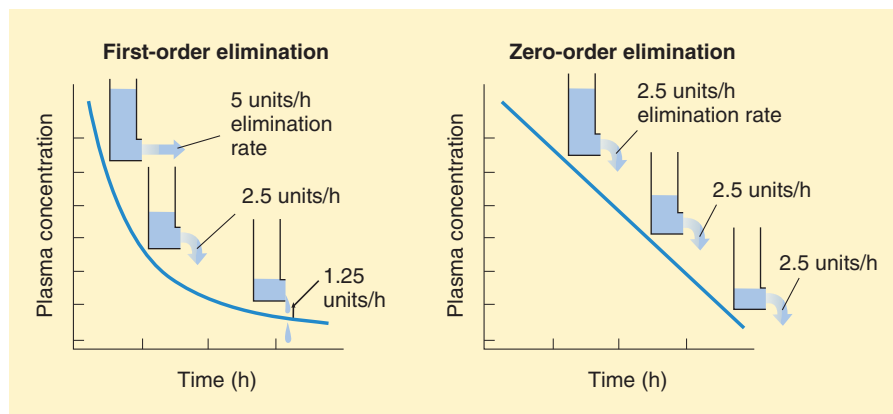
FIGURE 1–3 Comparison of first-order and zero-order elimination. For drugs with first-order kinetics (left), rate of elimination (units per hour) is proportional to concentration; this is the more common process. In the case of zero-order elimination (right), the rate is constant and independent of concentration.

Elimination of Drugs

Along with the dosage, the rate of elimination following the last dose (disappearance of the active molecules from the site of action, the bloodstream, and the body) determines the duration of action for many drugs. Therefore, knowledge of the time course of concentration in plasma is one factor used in predicting the intensity and duration of effect for most drugs. ***Note:*** Drug *elimination* is not the same as drug *excretion:* A drug may be eliminated by metabolism long before the modified molecules are excreted from the body. For most drugs and their metabolites, excretion is primarily by way of the kidney. Volatile anesthetic gases, a major exception, are excreted primarily by the lungs. For drugs with active metabolites (eg, diazepam), elimination of the parent molecule by metabolism is not synonymous with termination of action. For drugs that are not metabolized, excretion is the mode of elimination. A small number of drugs combine irreversibly with their receptors, so that disappearance from the bloodstream is not equivalent to cessation of drug action: These drugs may have a very prolonged action. For example, phenoxybenzamine, an irreversible inhibitor of α adrenoceptors, is eliminated from the bloodstream in less than 1 h after administration. The drug's action, however, lasts for 48 h, the time required for turnover of the receptors.

A. First-Order Elimination

The term *first-order elimination* indicates that the rate of elimination is proportional to the concentration (ie, the higher the concentration, the greater the amount of drug eliminated per unit time). The result is that the drug's concentration in plasma decreases exponentially with time (Figure 1–3, left). Drugs with first-order elimination have a characteristic **half-life of elimination** that is constant regardless of the amount of drug in the body. The concentration of such a drug in the blood will decrease by 50% for every half-life. Most drugs in clinical use demonstrate first-order kinetics.

B. Zero-Order Elimination

The term *zero-order elimination* implies that the rate of elimination is constant regardless of concentration (Figure 1–3, right).

This occurs with drugs that saturate their elimination mechanisms at concentrations of clinical interest. As a result, the concentrations of these drugs in plasma decrease in a linear fashion over time. Such drugs do not have a constant half-life. This is typical of ethanol (over most of its plasma concentration range) and of phenytoin and aspirin at high therapeutic or toxic concentrations.

Pharmacokinetic Models

A. Multicompartment Distribution

After absorption into the circulation, many drugs undergo an early distribution phase followed by a slower elimination phase. Mathematically, this behavior can be simulated by means of a "two-compartment model" as shown in Figure 1–4. The two compartments consist of the blood and the extravascular tissues. (Note that each phase is associated with a characteristic half-life: $t_{1/2\alpha}$ for the first phase, $t_{1/2\beta}$ for the second phase. Note also that when concentration is plotted on a logarithmic axis, the elimination phase for a first-order drug is a straight line.)

B. Other Distribution Models

A few drugs behave as if they were distributed to only 1 compartment (eg, if they are restricted to the vascular compartment). Others have more complex distributions that require more than 2 compartments for construction of accurate mathematical models.

■ II. DRUG DEVELOPMENT & REGULATION

The sale and use of drugs are regulated in most countries by governmental agencies. In the United States, regulation is by the **Food and Drug Administration (FDA).** New drugs are developed in industrial or academic laboratories. Before a new drug can be approved for regular therapeutic use in humans, a series of animal and experimental human studies **(clinical trials)** must be carried out.
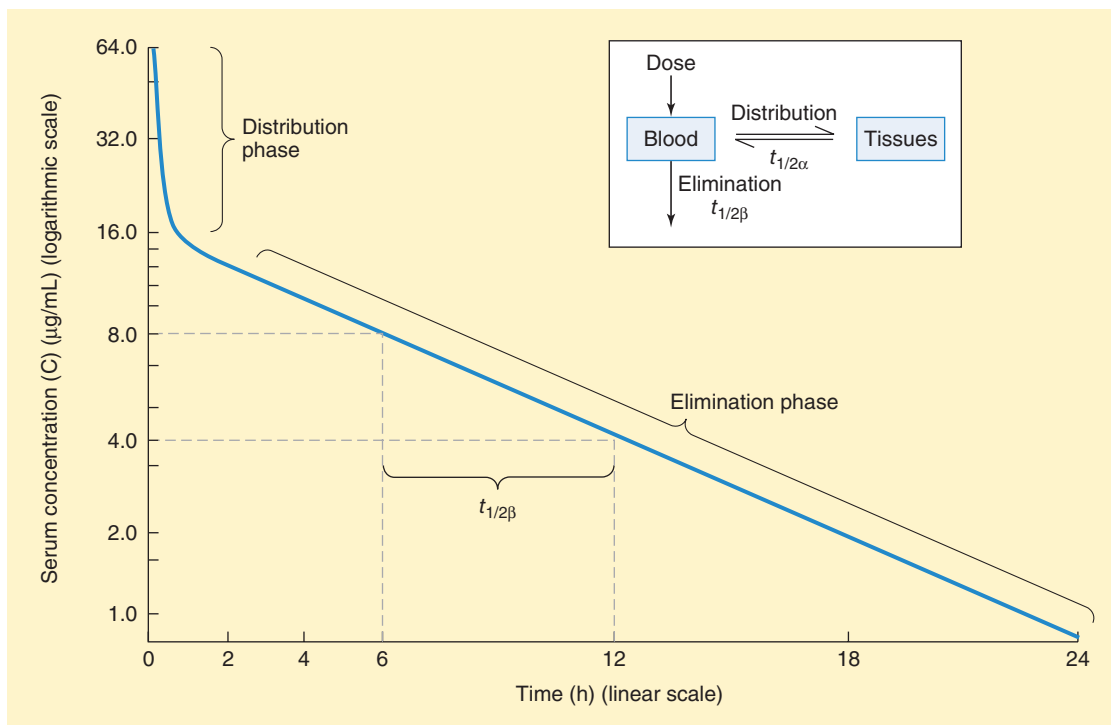
FIGURE 1–4 Serum concentration-time curve after administration of a drug as an intravenous bolus. This drug follows first-order kinetics and appears to occupy 2 compartments. The initial curvilinear portion of the data represents the distribution phase, with drug equilibrating between the blood compartment and the tissue compartment. The linear portion of the curve represents drug elimination. The elimination half-life ($t_{1/2\beta}$) can be extracted graphically as shown by measuring the time between any 2 plasma concentration points on the elimination phase that differ by twofold. (See Chapter 3 for additional details.)

New drugs may emerge from a variety of sources. Some are the result of identification of a new target for a disease. Rational molecular design or screening is then used to find a molecule that selectively alters the function of the target. New drugs may result from the screening of hundreds of compounds against model diseases in animals. In contrast, many so-called "me-too" drugs are the result of simple chemical alteration of the pharmacokinetic properties of an original prototype agent.

SAFETY & EFFICACY

Because society expects prescription drugs to be safe and effective, governments regulate the development and marketing of new drugs. Current regulations in the USA require evidence of relative safety (derived from acute and subacute toxicity testing in animals) and probable therapeutic action (from the pharmacologic profile in animals) before human testing is permitted. Some information about the pharmacokinetics of a compound is also required before clinical evaluation is begun. Chronic toxicity test *results* are generally not required, but testing must be underway before human studies are started. The development of a new drug and its pathway through various levels of testing and regulation are illustrated in Figure 1–5. The cost of development of a new drug, including false starts and discarded molecules, may be

greater than $500 million although the true cost is often hidden by the manufacturer.

ANIMAL TESTING

The animal testing of a specific drug that is required before human studies can begin is a function of its proposed use and the urgency of the application. Thus, a drug proposed for occasional topical use requires less extensive testing than one destined for chronic systemic administration.

Because of the urgent need, anticancer drugs and some antiviral drugs require less evidence of safety than do drugs used in treatment of less threatening diseases. Urgently needed drugs are often investigated and approved on an accelerated schedule.

A. Acute Toxicity

Acute toxicity studies are required for all new drugs. These studies involve administration of incrementing doses of the agent up to the lethal level in at least 2 species (eg, 1 rodent and 1 nonrodent).

B. Subacute and Chronic Toxicity

Subacute and chronic toxicity testing is required for most agents, especially those intended for chronic use. Doses are selected based on the results of acute tests. Tests are usually conducted
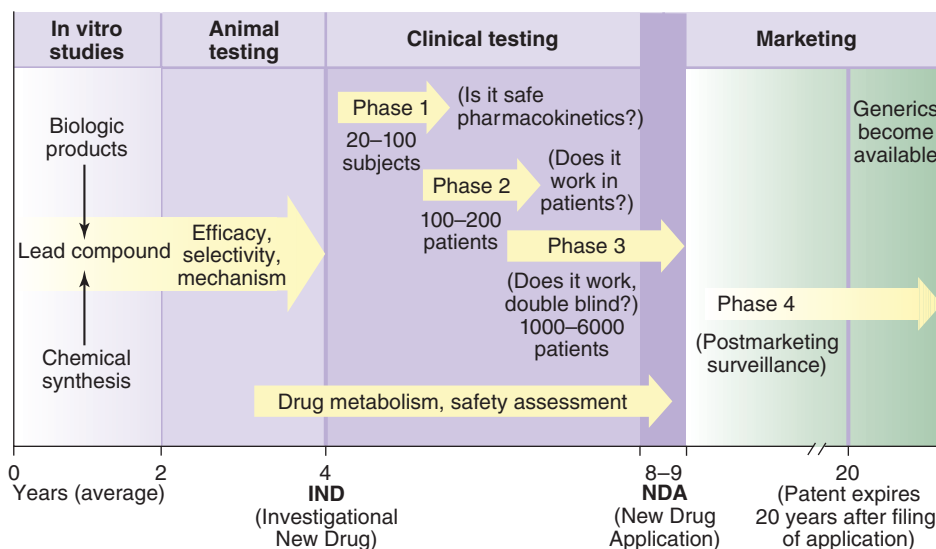
FIGURE 1–5 The development and testing process required to bring a new drug to market in the United States. Some requirements may be different for drugs used in life-threatening diseases. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 5–1.)

for 2–4 weeks (subacute) and 6–24 months (chronic), in at least 2 species.

TYPES OF ANIMAL TESTS

A. Pharmacologic Profile

The pharmacologic profile is a description of all the pharmacologic effects of a drug (eg, effects on cardiovascular function, gastrointestinal activity, respiration, hepatic and renal function, endocrine function, CNS). Both graded and quantal dose-response data are gathered.

B. Reproductive Toxicity

Reproductive toxicity testing involves the study of the fertility effects of the candidate drug and its teratogenic and mutagenic toxicity. Until 2015, the FDA had used a 5-level (A, B, C, D, X) minimally descriptive scale to summarize information regarding the safety of drugs in pregnancy (Table 1–3). For drugs submitted after June 2015, the letter scale has been abolished in favor of a narrative description of the safety or hazards of each drug, and separate categories are established for pregnancy, lactation, and for males and females of reproductive potential. The new system is designated the **Pregnancy and Lactation Labeling Rule (PLLR)** and is set forth at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm. New labeling for drugs approved after 2001 will be phased in. **Teratogenesis** can be defined as the induction of developmental defects in the somatic tissues of the fetus (eg, by exposure of the fetus to a chemical, infection, or radiation). Teratogenesis is studied by treating pregnant female animals of at least 2 species at selected times during early pregnancy when organogenesis is known to take place and by later examining the fetuses or neonates for abnormalities. Examples

TABLE 1–3 FDA ratings of drug safety in pregnancy.*

Category	Description
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote
B	Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters)
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only when the potential benefit justifies the potential risk to the fetus
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective)
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant

*Because of lack of definitive evidence for many drugs, many experts consider the A through X ranking system to be too simplistic and inaccurate; they prefer more detailed narrative descriptions of evidence available for each drug in question. See Pregnancy and Lactation Labeling Rule, text.

of drugs known to have teratogenic effects include thalidomide, isotretinoin, valproic acid, ethanol, glucocorticoids, warfarin, lithium, and androgens. **Mutagenesis** denotes induction of changes in the genetic material of animals of any age and therefore induction of heritable abnormalities. The **Ames test,** the standard in vitro test for mutagenicity, uses a special strain of salmonella bacteria whose growth depends on specific nutrients in the culture medium. Loss of this dependence as a result of exposure to the test drug signals a mutation. Many carcinogens (eg, aflatoxin, cancer chemotherapeutic drugs, and other agents that bind to DNA) have mutagenic effects and test positive in the Ames test. The **dominant lethal test** is an in vivo mutagenicity test carried out in mice. Male animals are exposed to the test substance before mating. Abnormalities in the results of subsequent mating (eg, loss of embryos, deformed fetuses) signal a mutation in the male's germ cells.

C. Carcinogenesis

Carcinogenesis is the induction of malignant characteristics in cells. Carcinogenicity is difficult and expensive to study, and the Ames test is often used to screen chemicals because there is a moderately high degree of correlation between mutagenicity in the Ames test and carcinogenicity in some animal tests, as previously noted. Agents with known carcinogenic effects include coal tar, aflatoxin, dimethylnitrosamine and other nitrosamines, urethane, vinyl chloride, and the polycyclic aromatic hydrocarbons in tobacco smoke (eg, benzo[*a*]pyrene) and other tobacco products.

CLINICAL TRIALS

Human testing of new drugs in the United States requires approval by institutional committees that monitor the ethical (informed consent, patient safety) and scientific aspects (study design, statistical power) of the proposed tests. Such testing also requires the prior approval by the FDA of an **Investigational New Drug (IND) Exemption application,** which is submitted by the developer to the FDA (Figure 1–5). The IND includes all the preclinical data collected up to the time of submission and the detailed proposal for clinical trials. The major clinical testing process is usually divided into 3 phases that are carried out to provide information for a **New Drug Application (NDA).** The NDA includes all the results of preclinical and clinical testing and constitutes the request for FDA approval of general marketing of the new agent for prescription use. A fourth phase of study (the surveillance phase) follows NDA approval. In particularly lethal conditions, the FDA may permit carefully monitored treatment of patients before phases 2 and 3 are completed.

A. Phase 1

A phase 1 trial consists of careful evaluation of the dose-response relationship and the pharmacokinetics of the new drug in a small number of *normal* human volunteers (eg, 20–100). An exception is the phase 1 trials of cancer chemotherapeutic agents and other highly toxic drugs; these are carried out by administering the agents to volunteer patients with the target disease. In phase 1 studies, the acute effects of the agent are studied over a broad range of dosages, starting with one that produces no detectable effect and progressing to one that produces either a significant physiologic response or a very minor toxic effect.

B. Phase 2

A phase 2 trial involves evaluation of a drug in a moderate number of *sick* patients (eg, 100–200) with the target disease. A placebo or positive control drug is included in a single-blind or double-blind design. The study is carried out under very carefully controlled conditions, and patients are closely monitored, often in a hospital research ward. The goal is to determine whether the agent has the desired efficacy (ie, produces adequate therapeutic response) at doses that are tolerated by sick patients. Detailed data are collected regarding the pharmacokinetics and pharmacodynamics of the drug in this patient population.

C. Phase 3

A phase 3 trial usually involves many patients (eg, 1000–6000 or more, in many centers) and many clinicians who are using the drug in the manner proposed for its ultimate general use (eg, in outpatients). Such studies usually include placebo and positive controls in a double-blind crossover design. The goals are to explore further, under the conditions of the proposed clinical use, the spectrum of beneficial actions of the new drug, to compare it with placebo (negative control) and older therapy (positive control), and to discover toxicities, if any, that occur so infrequently as to be undetectable in phase 2 studies. Very large amounts of data are collected and these studies are usually very expensive. Unfortunately, relatively few phase 3 trials include the current standard of care as a positive control.

If the drug successfully completes phase 3, an NDA is submitted to the FDA. If the NDA is approved, the drug can be marketed and phase 4 begins.

D. Phase 4

Phase 4 represents the postmarketing surveillance phase of evaluation, in which it is hoped that toxicities that occur very infrequently will be detected and reported early enough to prevent major therapeutic disasters. Manufacturers are required to inform the FDA at regular intervals of all reported untoward drug reactions. Unlike the first 3 phases, phase 4 has not been rigidly regulated by the FDA in the past. Because so many drugs have been found to be unacceptably toxic only after they have been marketed, there is considerable current interest in making phase 4 surveillance more consistent, effective, and informative.

E. Adaptive Clinical Trials

Because the traditional 3-phase clinical trials are often prolonged and expensive, a newer type of clinical trial is currently under development. Adaptive trials are aimed at combining 2 or more of the traditional phases and altering conditions, dosage, and targets as the trial progresses, based on data being collected.

DRUG PATENTS & GENERIC DRUGS

A patent application is usually submitted around the time that a new drug enters animal testing (Figure 1–5). In the United States, approval of the patent and completion of the NDA approval process give the originator the right to market the drug without competition from other firms for a period of 10–14 years from the NDA approval date. After expiration of the patent, any company may apply to the FDA for permission to market a generic version of the same drug if they demonstrate that their generic drug molecule is **bioequivalent** (ie, meets certain requirements for content, purity, and bioavailability) to the original product.

DRUG LEGISLATION

Many laws regulating drugs in the United States were passed during the 20th century. Refer to Table 1–4 for a partial list of this legislation.

ORPHAN DRUGS

An orphan drug is a drug for a rare disease (in the United States, defined as one affecting fewer than 200,000 people). The study of such agents has often been neglected because profits from the sales of an effective agent for an uncommon ailment might not pay the costs of development. In the United States, current legislation provides for tax relief and other incentives designed to encourage the development of orphan drugs.

TABLE 1–4 **Selected legislation pertaining to drugs in the United States.**

Law	Purpose and Effect
Pure Food and Drug Act of 1906	Prohibited mislabeling and adulteration of foods and drugs (but no requirement for efficacy or safety)
Harrison Narcotics Act of 1914	Established regulations for the use of opium, opioids, and cocaine (marijuana added in 1937)
Food, Drug, and Cosmetics Act of 1938	Required that new drugs be tested for safety as well as purity
Kefauver-Harris Amendment (1962)	Required proof of efficacy as well as safety for new drugs
Dietary Supplement and Health Education Act (1994)	Amended the Food, Drug, and Cosmetics Act of 1938 to establish standards for dietary supplements but prohibited the FDA from applying drug efficacy and safety standards to supplements

QUESTIONS

1. A 3-year-old is brought to the emergency department having just ingested a large overdose of chlorpropamide, an oral antidiabetic drug. Chlorpropamide is a weak acid with a pK_a of 5.0. It is capable of entering most tissues. On physical examination, the heart rate is 110/min, blood pressure 90/50 mm Hg, and respiratory rate 30/min. Which of the following statements about this case of chlorpropamide overdose is most correct?
   - **(A)** Urinary excretion would be accelerated by administration of NH_4Cl, an acidifying agent
   - **(B)** Urinary excretion would be accelerated by giving $NaHCO_3$, an alkalinizing agent
   - **(C)** Less of the drug would be ionized at blood pH than at stomach pH
   - **(D)** Absorption of the drug would be slower from the stomach than from the small intestine

2. Botulinum toxin is a large protein molecule. Its action on cholinergic transmission depends on an intracellular action within nerve endings. Which one of the following processes is best suited for permeation of very large protein molecules into cells?
   - **(A)** Aqueous diffusion
   - **(B)** Endocytosis
   - **(C)** First-pass effect
   - **(D)** Lipid diffusion
   - **(E)** Special carrier transport

3. A 12-year-old child has bacterial pharyngitis and is to receive an oral antibiotic. She complains of a sore throat and pain on swallowing. The tympanic membranes are slightly reddened bilaterally, but she does not complain of earache. Blood pressure is 105/70 mm Hg, heart rate 100/min, temperature 37.8°C (100.1°F). Ampicillin is a weak organic acid with a pK_a of 2.5. What percentage of a given dose will be in the lipid-soluble form in the duodenum at a pH of 4.5?
   - **(A)** About 1%
   - **(B)** About 10%
   - **(C)** About 50%
   - **(D)** About 90%
   - **(E)** About 99%

4. Ampicillin is eliminated by first-order kinetics. Which of the following statements best describes the process by which the plasma concentration of this drug declines?
   - **(A)** There is only 1 metabolic path for drug elimination
   - **(B)** The half-life is the same regardless of the plasma concentration
   - **(C)** The drug is largely metabolized in the liver after oral administration and has low bioavailability
   - **(D)** The rate of elimination is proportional to the rate of administration at all times
   - **(E)** The drug is distributed to only 1 compartment outside the vascular system

5. The pharmacokinetics of a new drug are under study in a phase 1 clinical trial. Which statement about the distribution of drugs to specific tissues is most correct?
   (A) Distribution to an organ is independent of blood flow
   (B) Distribution of a lipid-soluble drug will be to adipose tissue initially
   (C) Distribution into a tissue depends on the unbound drug concentration gradient between blood and the tissue
   (D) Distribution is increased for drugs that are strongly bound to plasma proteins
   (E) Distribution has no effect on the half-life of the drug

6. The pharmacokinetic process or property that distinguishes the elimination of ethanol and high doses of phenytoin and aspirin from the elimination of most other drugs is called
   (A) Distribution
   (B) Excretion
   (C) First-pass effect
   (D) First-order elimination
   (E) Zero-order elimination

7. Which of the following statements about animal testing of potential new therapeutic agents is *most* correct?
   (A) Requires at least 3 years to discover late toxicities
   (B) Requires at least 1 primate species (eg, rhesus monkey)
   (C) Requires the submission of histopathologic slides and specimens to the FDA for evaluation by government scientists
   (D) Has good predictability for drug allergy-type reactions
   (E) May be abbreviated in the case of some very toxic agents used in cancer

8. The "dominant lethal" test involves the treatment of a male adult animal with a chemical before mating; the pregnant female is later examined for fetal death and abnormalities. The dominant lethal test therefore is a test of
   (A) Teratogenicity
   (B) Mutagenicity
   (C) Carcinogenicity
   (D) Sperm viability

9. In a phase 1 clinical trial, "Novexum," a new drug, was administered intravenously to 25 volunteers, and blood samples were taken for several hours. Several inactive metabolites were found as well as declining concentrations of Novexum. A graph was prepared as shown below, with the Novexum plasma levels plotted on a logarithmic ordinate and time on a linear abscissa. It was concluded that the drug has first-order kinetics. From this graph, what is the best estimate of the elimination half-life of Novexum?
   (A) 0.5 h
   (B) 1 h
   (C) 3 h
   (D) 4 h
   (E) 7 h
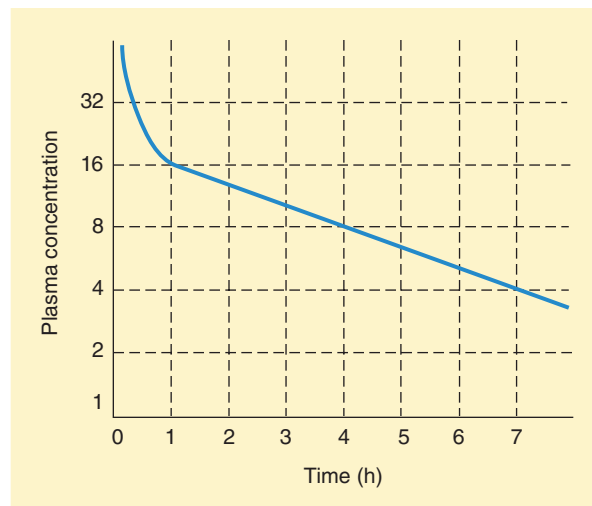
10. A large pharmaceutical company has conducted extensive animal testing of a new drug for the treatment of advanced prostate cancer. The chief of research and development recommends that the company now submit an IND application in order to start clinical trials. Which of the following statements is *most* correct regarding clinical trials of new drugs?
    (A) Phase 1 involves the study of a small number of normal volunteers by highly trained clinical pharmacologists
    (B) Phase 2 involves the use of the new drug in a large number of patients (1000–5000) who have the disease to be treated under conditions of proposed use (eg, outpatients)
    (C) Chronic animal toxicity studies must be complete and reported in the IND
    (D) Phase 4 involves the detailed study of toxic effects that have been discovered in phase 3
    (E) Phase 2 requires the use of a positive control (a known effective drug) and a placebo

11. Which of the following would probably *not* be included in an optimal phase 3 clinical trial of a new analgesic drug for mild pain?
    (A) A negative control (placebo)
    (B) A positive control (current standard analgesic therapy)
    (C) Double-blind protocol (in which neither the patient nor immediate observers of the patient know which agent is active)
    (D) A group of 1000–5000 subjects with a clinical condition requiring analgesia
    (E) Prior submission of an NDA (new drug application) to the FDA

12. The Ames test is frequently carried out before clinical trials are begun. The Ames test is a method that detects
    (A) Carcinogenesis in primates
    (B) Carcinogenesis in rodents
    (C) Mutagenesis in bacteria
    (D) Teratogenesis in any mammalian species
    (E) Teratogenesis in primates

13. Which of the following statements about new drug development is *most* correct?
    (A) If the need is great, drugs that test positive for teratogenicity, mutagenicity, or carcinogenicity can be tested in humans but the IND must specify safety measures to be taken
    (B) Food supplements and herbal (botanical) remedies must be shown to be effective for the target condition before marketing is approved by the FDA
    (C) All new drugs must be studied in at least 1 primate species before NDA submission
    (D) Orphan drugs are drugs that are no longer produced by the original manufacturer
    (E) Phase 4 (surveillance) is the most rigidly regulated phase of clinical drug trials

14. Which statement about the development of new drugs is most correct?
    (A) Because they may cause anaphylaxis, proteins cannot be used as drugs
    (B) Most drugs fall between 100 and 1000 in molecular weight
    (C) Drugs for systemic action that are to be administered orally should be highly water soluble and insoluble in lipids
    (D) Water solubility is minimal in highly polarized (charged) drug molecules

ANSWERS

1. Questions that deal with acid-base (Henderson-Hasselbalch) manipulations are common on examinations. Since absorption involves permeation across lipid membranes, we can in theory treat an overdose by decreasing absorption from the gut and reabsorption from the tubular urine by making the drug *less lipid-soluble.* Ionization attracts water molecules and decreases lipid solubility. Chlorpropamide is a weak acid, which means that it is less ionized when protonated, ie, at acid pH. Choice **C** suggests that the drug would be less ionized at pH 7.4 than at pH 2.0, which is clearly wrong for weak acids. Choice **D** says (in effect) that the more ionized form is absorbed faster, which is incorrect. **A** and **B** are opposites because NH_4Cl is an acidifying salt and sodium bicarbonate an alkalinizing one. (From the point of view of test strategy, opposites in a list of answers always deserve careful attention.) Because an alkaline environment favors ionization of a weak acid, we should give bicarbonate. The answer is **B**. Note that clinical management of overdose involves many other considerations in addition to trapping the drug in urine; manipulation of urine pH may be contraindicated for other reasons.

2. Endocytosis is an important mechanism for transport of very large molecules across membranes. Aqueous diffusion is not involved in transport across the lipid barrier of cell membranes. Lipid diffusion and special carrier transport are common for smaller molecules. The first-pass effect has nothing to do with the mechanisms of permeation; rather, it denotes drug metabolism or excretion before absorption into the systemic circulation. The answer is **B**.

3. U.S. Medical Licensing Examination (USMLE)-type questions often contain a lengthy clinical description in the stem. One can often determine the relevance of the clinical data by scanning the last sentence in the stem and the list of answers, see Appendix I. In this question, the emphasis is clearly on pharmacokinetic principles. Ampicillin is an acid, so it is more ionized at alkaline pH and less ionized at acidic pH. The Henderson-Hasselbalch equation predicts that the ratio changes from 50/50 at the pH equal to the pK_a to 1/10 (protonated/unprotonated) at 1 pH unit more alkaline than the pK_a and 1/100 at 2 pH units more alkaline. For acids, the protonated form is the nonionized, more lipid-soluble form. The answer is **A**.

4. "First-order" means that the elimination rate is proportional to the concentration perfusing the organ of elimination. The half-life is a constant. The rate of elimination is proportional to the rate of administration only at steady state. The order of elimination is independent of the number of compartments into which a drug distributes. The answer is **B**.

5. This is a straightforward question of pharmacokinetic distribution concepts. Choice B is incorrect because distribution depends on blood flow as well as solubility in the tissue; thus most drugs will initially distribute to high blood flow tissues and only later to larger, low-flow tissues, even if they are more soluble in them. From the list of determinants of drug distribution given on pages 5–6, choice **C** is correct.

6. The excretion of most drugs follows first-order kinetics. However, ethanol and, in higher doses, aspirin and phenytoin follow zero-order kinetics; that is, their elimination rates are constant regardless of blood concentration. The answer is **E**.

7. Drugs proposed for short-term use may not require long-term chronic testing. For some drugs, no primates are used; for other agents, only 1 species is used. The data from the tests, not the evidence itself, must be submitted to the FDA. Prediction of human drug allergy from animal testing is useful but not definitive (see answer 12). Testing may be abbreviated for drugs for which there is urgent need; the answer is **E**.

8. The description of the test indicates that a chromosomal change (passed from father to fetus) is the toxicity detected. This is a mutation. The answer is **B**.

9. Drugs with first-order kinetics have constant half-lives, and when the log of the concentration in a body compartment is plotted versus time, a straight line results. The half-life is defined as the time required for the concentration to decrease by 50%. As shown in the graph, the concentration of Novexum decreased from 16 units at 1 h to 8 units at 4 h and 4 units at 7 h; therefore, the half-life is 7 h minus 4 h or 3 h. The answer is **C**.

10. Except for known toxic drugs (eg, cytotoxic cancer chemotherapy drugs), phase 1 is carried out in 25–50 normal volunteers. Phase 2 is carried out in several hundred closely monitored patients with the disease. Results of chronic toxicity studies in animals are required in the NDA and are usually underway at the time of IND submission. However, they do not have to be completed and reported in the IND. Phase 4 is the general surveillance phase that follows marketing of the new drug. It is not targeted at specific effects. Positive controls and placebos are not a rigid requirement of any phase of clinical trials, although placebos are often used in phase 2 and phase 3 studies. The answer is **A**.

11. The first 4 items (**A–D**) are correct; they *would* be included. An NDA cannot be acted upon until the first 3 phases of clinical trials have been completed. (The IND must be approved before clinical trials can be conducted.) The answer is **E**.

12. The Ames test is carried out in *Salmonella* and detects mutations in the bacterial DNA. Because mutagenic potential is associated with carcinogenic risk for many chemicals, a positive Ames test is often used to suggest that a particular agent may be a carcinogen. However, the test itself only detects mutations. The answer is **C.**

13. Food supplements and botanicals are much more loosely regulated than conventional drugs; they are not required to be shown effective before marketing. Primates are not required in any phase of new drug testing, although they are sometimes used. (Note the trigger word "all" in choice (C); answers claiming "all…" are almost always wrong.) Orphan drugs are those for which the anticipated patient population is smaller than 200,000 patients in the United States. Phase 4 surveillance is the most loosely regulated phase of clinical trials. Many drugs in current clinical use test positive for teratogenicity, mutagenicity, or carcinogenicity. Such drugs are usually labeled with warnings about these toxicities and, in the case of teratogenicity, are labeled as contraindicated in pregnancy. The answer is **A.**

14. Many peptide and protein drugs, eg, insulin, antibodies, are in use; if identical or sufficiently similar to the human molecules, anaphylaxis is uncommon. Most drugs *do* fall between 100 and 1000 in molecular weight. Drugs for systemic use should be at least minimally water soluble (so they do not precipitate in the intestine) and lipid soluble (so they can cross lipid barriers). Charged molecules attract a shell of water molecules, making them more water soluble. The answer is **B.**

CHECKLIST

When you complete this chapter, you should be able to:

❑ Define and describe the terms *receptor* and *receptor site*.

❑ Distinguish between a competitive inhibitor and an allosteric inhibitor.

❑ Predict the relative ease of permeation of a weak acid or base from knowledge of its pK_a, the pH of the medium, and the Henderson-Hasselbalch equation.

❑ List and discuss the common routes of drug administration and excretion.

❑ Draw graphs of the blood level versus time for drugs subject to zero-order elimination and for drugs subject to first-order elimination. Label the axes appropriately.

❑ Describe the major animal and clinical studies carried out in drug development.

❑ Describe the purpose of the Investigational New Drug (IND) Exemption and the New Drug Application (NDA).

❑ Define carcinogenesis, mutagenesis, and teratogenesis.

❑ Describe the difference between the FDA regulations for ordinary drugs and those for botanical remedies.

CHAPTER 1 Summary Table

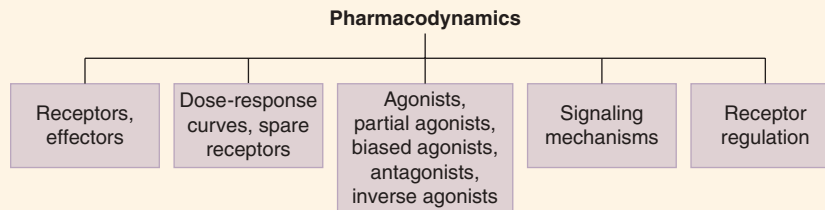| Major Concept	Description
Nature of drugs	Drugs are chemicals that modify body functions. They may be ions, carbohydrates, lipids, or proteins. They vary in size from lithium (MW 7) to proteins (MW ≥ 50,000)
Drug permeation	Most drugs are administered at a site distant from their target tissue. To reach the target, they must permeate through both lipid and aqueous pathways. Movement of drugs occurs by means of aqueous diffusion, lipid diffusion, transport by special carriers, or by exocytosis and endocytosis
Rate of diffusion	Aqueous diffusion and lipid diffusion are predicted by Fick's law and are directly proportional to concentration gradient, area, and permeability coefficient and inversely proportional to the length or thickness of the diffusion path
Drug trapping	Because the permeability coefficient of a weak base or weak acid varies with the pH according to the Henderson-Hasselbalch equation, drugs may be trapped in a cellular compartment in which the pH is such as to reduce their solubility in the barriers surrounding the compartment

(Continued)

CHAPTER 1 Summary Table (*Continued*)

Major Concept	Description
Routes of administration	Drugs are usually administered by one of the following routes of administration: oral, buccal, sublingual, topical, transdermal, intravenous, subcutaneous, intramuscular, rectal, or by inhalation
Drug distribution	After absorption, drugs are distributed to different parts of the body depending on concentration gradient, blood flow, solubility, and binding in the tissue
Drug elimination	Drugs are eliminated by reducing their concentration or amount in the body. This occurs when the drug is inactivated by metabolism or excreted from the body
Elimination kinetics	The rate of elimination of drugs may be zero order (ie, constant regardless of concentration) or first order (ie, proportional to the concentration)
Drug safety and efficacy	Standards of safety and efficacy for drugs developed slowly during the 20th century and are still incomplete. Because of heavy lobbying by manufacturers, these standards are still not applied to nutritional supplements and many so-called *botanical* or *herbal medications*. A few of the relevant US laws are listed in Table 1–4
Preclinical drug testing	All new drugs undergo extensive preclinical testing in isolated tissue preparations and cell cultures, isolated animal organ preparations, and intact animals. Experiments are carried out to determine the full range of toxic and therapeutic effects. See Figure 1–5
Clinical drug trials	In the USA, all new drugs proposed for use in humans must undergo a series of tests in humans. These tests are regulated by the FDA and may be accelerated or prolonged depending on the perceived clinical need and possible toxicities. The trials are often divided into 3 phases before marketing is allowed. See Figure 1–5

Pharmacodynamics

Pharmacodynamics deals with the effects of drugs on biologic systems, whereas pharmacokinetics (Chapter 3) deals with actions of the biologic system on the drug. The principles of pharmacodynamics apply to all biologic systems, from isolated receptors in the test tube to patients with specific diseases.

Pharmacodynamics

Receptors, effectors	Dose-response curves, spare receptors	Agonists, partial agonists, biased agonists, antagonists, inverse agonists	Signaling mechanisms	Receptor regulation

RECEPTORS

Receptors are the specific molecules in a biologic system with which drugs interact to produce changes in the function of the system. Receptors must be **selective** in their ligand-binding characteristics (so as to respond to appropriate chemical signals and not to meaningless ones). Receptors must also be **modifiable** when they bind a drug molecule (so as to bring about a change in function). Many receptors have been identified, purified, chemically characterized, and cloned. Most are proteins; a few are other macromolecules such as DNA. Some authorities consider enzymes as a separate category; for the purposes of this book, enzymes that are affected by drugs are considered receptors. The **receptor site** (also known as the **recognition site**) for a drug is the specific binding region of the receptor macromolecule and has a relatively high and selective affinity for the drug molecule. The interaction of a drug with its receptor is the fundamental event that initiates the action of the drug, and many drugs are classified on the basis of their primary receptor affinity.

EFFECTORS

Effectors are molecules that translate the drug-receptor interaction into a change in cellular activity. The best examples of effectors are enzymes such as adenylyl cyclase. Some receptors are also effectors in that a single molecule may incorporate both the drug-binding site and the effector mechanism. For example, a tyrosine kinase effector enzyme is part of the insulin receptor molecule, and a sodium-potassium channel is the effector part of the nicotinic acetylcholine receptor.
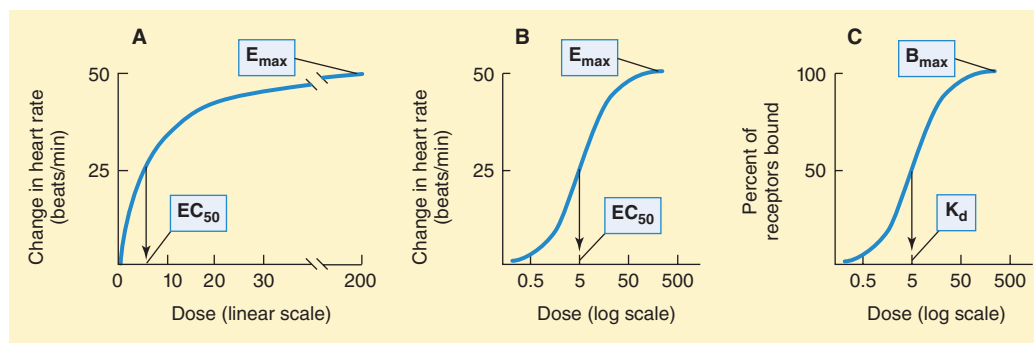
GRADED DOSE-RESPONSE RELATIONSHIPS

When the response of a particular receptor-effector system is measured against increasing concentrations of a drug, the graph of the response versus the drug concentration or dose is called a *graded dose-response curve* (Figure 2–1A). Plotting the same data on a logarithmic concentration axis usually results in a sigmoid curve, which simplifies the mathematical manipulation of the dose-response data (Figure 2–1B). The efficacy (E_{max}) and potency (EC_{50} or ED_{50}) parameters are derived from these data. The *smaller* the EC_{50} (or ED_{50}), the *greater* the potency of the drug.

GRADED DOSE-BINDING RELATIONSHIP & BINDING AFFINITY

It is possible to measure the percentage of receptors bound by a drug, and by plotting this percentage against the log of the concentration of the drug, a *dose-binding* graph similar to the

High-Yield Terms to Learn

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Receptor	A molecule to which a drug binds to bring about a change in function of the biologic system
Inert binding molecule or site	A molecule to which a drug may bind without changing any function
Receptor site	Specific region of the receptor molecule to which the drug binds
Spare receptor	Receptor that does not bind drug when the drug concentration is sufficient to produce maximal effect; present if $K_d > EC_{50}$
Effector	Component of a system that accomplishes the biologic effect after the receptor is activated by an agonist; often a channel, transporter, or enzyme molecule, may be part of the receptor molecule
Agonist	A drug that activates its receptor upon binding
Biased agonist	An agonist that activates the same receptor as other drugs in its group but also causes additional downstream effects that are not seen with other agonists in the group
Pharmacologic antagonist	A drug that binds to the receptor without activating it and thereby prevents activation by an agonist
Competitive antagonist	A pharmacologic antagonist that can be overcome by increasing the concentration of agonist
Irreversible antagonist	A pharmacologic antagonist that cannot be overcome by increasing agonist concentration
Physiologic antagonist	A drug that counters the effects of another by binding to a different receptor and causing opposing effects
Chemical antagonist	A drug that counters the effects of another by binding the agonist drug (not the receptor)
Allosteric agonist, antagonist	A drug that binds to a receptor molecule without interfering with normal agonist binding but alters the response to the normal agonist
Partial agonist	A drug that binds to its receptor but produces a smaller effect (E_{max}) at full dosage than a full agonist
Constitutive activity	Activity of a receptor-effector system in the *absence* of an agonist ligand
Inverse agonist	A drug that binds to the non-active state of receptor molecules and decreases constitutive activity (see text)
Graded dose-response curve	A graph of the increasing response to increasing drug concentration or dose
Quantal dose-response curve	A graph of the increasing fraction of a population that shows a specified response at progressively increasing doses
EC_{50}, ED_{50}, TD_{50}, etc	In graded dose-response curves, the concentration or dose that causes 50% of the maximal effect or toxicity. In quantal dose-response curves, the concentration or dose that causes a specified response in 50% of the population under study
K_d	The concentration of drug that binds 50% of the receptors in the system
Efficacy, maximal efficacy	The largest effect that can be achieved with a particular drug, regardless of dose, E_{max}
Potency	The amount or concentration of drug required to produce a specified effect, usually EC_{50} or ED_{50}

FIGURE 2–1 Graded dose-response and dose-binding graphs. (In isolated tissue preparations, *concentration* is usually used as the measure of dose.) **A.** Relation between drug dose or concentration (abscissa) and drug effect (ordinate). When the dose axis is linear, a hyperbolic curve is commonly obtained. **B.** Same data, logarithmic dose axis. The dose or concentration at which effect is half-maximal is denoted EC_{50}, whereas the maximal effect is E_{max}. **C.** If the percentage of receptors that bind drug is plotted against drug concentration, a similar curve is obtained, and the concentration at which 50% of the receptors are bound is denoted K_d, and the maximal number of receptors bound is termed B_{max}.

dose-response curve is obtained (Figure 2–1C). The concentration of drug required to bind 50% of the receptor sites is denoted by the dissociation constant (K_d) and is a useful measure of the affinity of a drug molecule for its binding site on the receptor molecule. The smaller the K_d, the greater the affinity of the drug for its receptor. If the number of binding sites on each receptor molecule is known, it is possible to determine the total number of receptors in the system from the B_{max}.

QUANTAL DOSE-RESPONSE RELATIONSHIPS

When the minimum dose required to produce a specified response is determined in each member of a population, the *quantal dose-response relationship* is defined (Figure 2–2). For example, a blood pressure-lowering drug might be studied by measuring the dose required to lower the mean arterial pressure by 20 mm Hg in 100 hypertensive patients. When plotted as the percentage of the population that shows this response at each dose versus the log of the dose administered, a cumulative quantal dose-response curve, usually sigmoid in shape, is obtained. The **median effective dose** (ED_{50}), **median toxic dose** (TD_{50}), and (in animals) **median lethal dose** (LD_{50}) are derived from experiments carried out in this manner. Because the magnitude of the specified effect is arbitrarily determined, the ED_{50} determined by quantal dose-response measurements has no direct relation to the ED_{50}
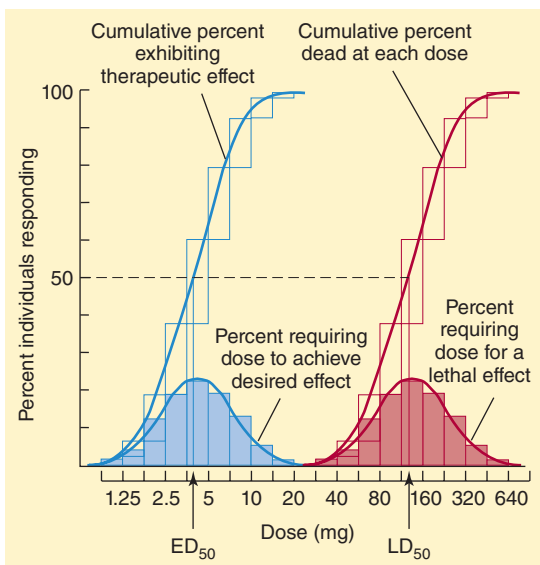
FIGURE 2–2 Quantal dose-response plots from a study of the therapeutic and lethal effects of a new drug in mice. Shaded boxes (and the accompanying bell-shaped curves) indicate the frequency distribution of doses of drug required to produce a specified effect, that is, the percentage of animals that required a particular dose to exhibit the effect. The open boxes (and corresponding sigmoidal curves) indicate the cumulative frequency distribution of responses, which are lognormally distributed. (Modified and reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 2–16.)

determined from graded dose-response curves. Unlike the graded dose-response determination, no attempt is made to determine the maximal effect of the drug. Quantal dose-response data provide information about the variation in sensitivity to the drug in a given population, and if the variation is small, the curve is steep.

EFFICACY

Efficacy—often called **maximal efficacy**—is the greatest effect (E_{max}) an agonist can produce if the dose is taken to the highest tolerated level. Efficacy is determined mainly by the nature of the drug and the receptor and its associated effector system. It can be measured with a graded dose-response curve (Figure 2–1) but not with a quantal dose-response curve. By definition, **partial agonists** have lower maximal efficacy than full agonists (see later discussion).

POTENCY

Potency denotes the amount of drug needed to produce a specified effect. In graded dose-response measurements, the effect usually chosen is 50% of the maximal effect and the concentration or dose causing this effect is called the EC_{50} or ED_{50} (Figure 2–1A and B). Potency is determined mainly by the affinity of the receptor for the drug and the number of receptors available. In quantal dose-response measurements, ED_{50}, TD_{50}, and LD_{50} are also potency variables (median effective, median toxic, and median lethal doses, respectively, in the population studied). Thus, a measure of potency can be specified using either graded or quantal dose-response curves (eg, Figures 2–1 and 2–2, respectively), but the numbers obtained are not identical and they have different meanings.

SPARE RECEPTORS

Spare receptors are said to exist if the maximal drug response (E_{max}) is obtained at less than 100% occupation of the receptors (B_{max}). In practice, the determination is usually made by comparing the concentration for 50% of maximal effect (EC_{50}) with the concentration for 50% of maximal binding (K_d). If the EC_{50} is less than the K_d, spare receptors are said to exist (Figure 2–3). This might result from 1 of 2 mechanisms. First, the duration of the *effector activation* may be much greater than the duration of the *drug-receptor* interaction. Second, the actual number of receptors may exceed the number of effector molecules available. The presence of spare receptors increases sensitivity to the agonist because the likelihood of a drug-receptor interaction increases in proportion to the number of receptors available. (For contrast, the system depicted in Figure 2–1, panels B and C, does not have spare receptors, since the EC_{50} and the K_d are equal.)

AGONISTS, PARTIAL AGONISTS, BIASED AGONISTS, & INVERSE AGONISTS

Current concepts of drug-receptor interactions consider the receptor to have at least 2 states—active and inactive. In the absence of ligand, a receptor might be fully active or completely inactive; alternatively,