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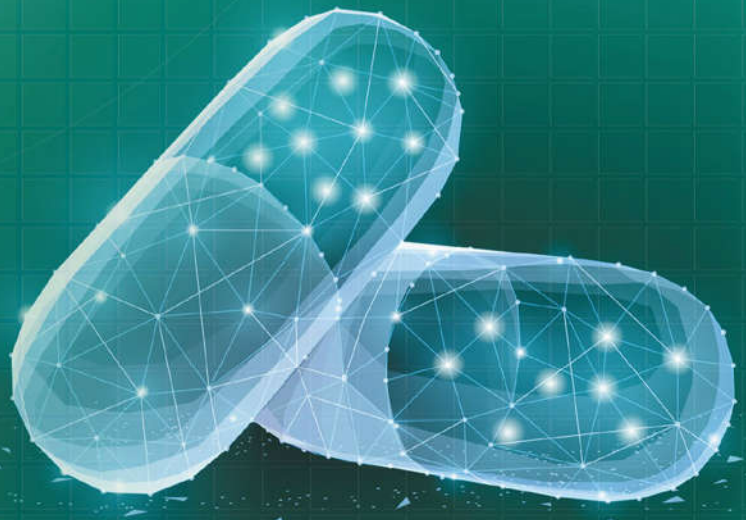
Pharmacology

SEVENTH EDITION

Sarah Lerchenfeldt



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Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Matt Hauber
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Prepress Vendor: SPi Global

Seventh Edition

9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data
Names: Lerchenfeldt, Sarah, author. | Preceded by (work): Rosenfeld, Gary C. Pharmacology.
Title: BRS pharmacology / Sarah Lerchenfeldt.
Other titles: Pharmacology
Description: Seventh edition. | Philadelphia : Wolters Kluwer, [2020] | Preceded by Pharmacology / Gary C. Rosenfeld, David S. Loose. 6th ed. 2014.
Identifiers: LCCN 2019013763 | ISBN 9781975105495
Subjects: | MESH: Pharmacological Phenomena | Pharmaceutical Preparations | Examination Question
Classification: LCC RM301.13 | NLM QV 18.2 | DDC 615.1076—dc23 LC record available at https://lccn.loc.gov/2019013763

shop.lww.com

Preface

This concise review of medical pharmacology is designed for health professions students, including medical students, dental students, and those enrolled in physician assistant or nurse practitioner programs. It is intended primarily to help students prepare for course examinations and licensing examinations, including the United States Medical Licensing Examination (USMLE) Step 1. This book presents condensed and succinct descriptions of relevant and current board-driven information pertaining to pharmacology without the usual associated details. It is not meant to be a substitute for the comprehensive presentation of information and difficult concepts found in standard pharmacology texts.

ORGANIZATION

The seventh edition begins with a chapter devoted to the general principles of drug action, followed by chapters concerned with drugs acting on the major body systems. Other chapters discuss anti-inflammatory and immunosuppressive agents, drugs used to treat anemia and disorders of hemostasis, infectious diseases, cancer, and toxicology.

Each chapter includes a presentation of specific drugs with a discussion of their general properties, mechanism of action, pharmacologic effects, therapeutic uses, and adverse effects. A drug list, tables, and figures summarize essential drug information included in all chapters.

Clinically oriented, USMLE-style review questions and answers with explanations follow each chapter to help students assess their understanding of the information. Similarly, a comprehensive examination consisting of USMLE-style questions is included at the end of the book. This examination serves as a self-assessment tool to help students determine their fund of knowledge and diagnose any weaknesses in pharmacology.

KEY FEATURES

- Updated with current drug information
- End-of-chapter review tests feature updated USMLE-style questions
- Several tables and figures summarize essential information for quick recall
- Updated drug lists for each chapter
- Additional USMLE-style comprehensive examination questions and explanations

Sarah Lerchenfeldt, PharmD

Acknowledgments

I would like to extend my sincere thanks to Dr. Gary C. Rosenfeld and Dr. David S. Loose for writing the first six editions of *BRS Pharmacology*. I would also like to thank the Wolters Kluwer staff and their associates for their contributions to this edition.

Contents

chapter 1

Fundamental Principles of Pharmacology

I. DOSE–RESPONSE RELATIONSHIPS

A. Drug effects. Drug effects are produced by altering the normal functions of cells and tissues in the body via one of the four general mechanisms:

1. *Interaction with receptors*

a. Receptors are naturally occurring target macromolecules that mediate the effects of endogenous physiologic substances such as neurotransmitters or hormones.

b. Figure 1.1 illustrates the four major classes of drug–receptor interactions, using specific examples of endogenous ligands.

(1) Ligand-activated ion channels. Figure 1.1A illustrates acetylcholine interacting with a nicotinic receptor that is a nonspecific Na^+/K^+ transmembrane ion channel. Interaction of a molecule of acetylcholine with each subunit of the channel produces a conformational change that permits the passage of sodium (Na^+) and potassium (K^+). Other channels that are targets for various drugs include specific calcium (Ca^{2+}) and K^+ channels.

(2) G-protein–coupled receptors (Fig. 1.1B–D). G-protein–coupled receptors compose the largest class of receptors. All the receptors have seven transmembrane segments, three intracellular loops, and an intracellular carboxy-terminal tail. The biologic activity of the receptors is mediated via interaction with a number of G (guanosine triphosphate binding) proteins.

(a) $G\alpha_s$-coupled receptors. Figure 1.1B illustrates that a β-adrenoceptor, which when activated by ligand binding (e.g., epinephrine), exchanges GDP for GTP. This facilitates the migration of $G\alpha_s$ ($G\alpha_{stimulatory}$) and its interaction with adenylyl cyclase (AC). $G\alpha_s$-bound AC catalyzes the production of cyclic AMP (cAMP) from adenosine triphosphate (ATP); cAMP activates protein kinase A, which subsequently acts to phosphorylate and activate a number of effector proteins. The βγ dimer may also activate some effectors. Hydrolysis of the guanosine triphosphate (GTP) bound to the Gα to guanosine diphosphate (GDP) terminates the signal.

(b) $G\alpha_i$ ($G\alpha_{inhibitory}$)-coupled receptors (Fig. 1.1C). Ligand binding (e.g., somatostatin) to $G\alpha_i$-coupled receptors similarly exchanges GTP for GDP, but $G\alpha_i$ inhibits AC, leading to reduced cAMP production.

(c) G_q (and G_{11})-coupled receptors (Fig. 1.1D). G_q (and G_{11}) interact with ligand (e.g., serotonin)-activated receptors and increase the activity of phospholipase C (PLC). PLC cleaves the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3). DAG activates protein kinase C, which can subsequently phosphorylate and activate a number of cellular proteins; IP_3 causes the release of Ca^{2+} from the endoplasmic reticulum into the cytoplasm, where it can activate many cellular processes.

(3) Receptor-activated tyrosine kinases (Fig. 1.1E). Many growth-related signals (e.g., insulin) are mediated via membrane receptors that possess intrinsic tyrosine kinase activity as illustrated for the insulin receptor. Ligand binding causes conformational changes in the receptor; some receptor tyrosine kinases are monomers that dimerize

upon ligand binding. The liganded receptors then autophosphorylate tyrosine residues, which recruit cytoplasmic proteins to the plasma membrane where they are also tyrosine phosphorylated and activated.

(4) **Intracellular nuclear receptors** (Fig. 1.1F). Ligands (e.g., cortisol) for nuclear receptors are lipophilic and can diffuse rapidly through the plasma membrane. In the absence of ligand, nuclear receptors are inactive because of their interaction with chaperone proteins such as heat-shock proteins like HSP-90. Binding of ligand promotes structural changes in the receptor that facilitate dissociation of chaperones, entry of receptors into the nucleus, hetero- or homodimerization of receptors, and high-affinity interaction with the DNA of target genes. DNA-bound nuclear receptors are able to recruit a diverse number of proteins called coactivators, which subsequently act to increase transcription of the target gene.

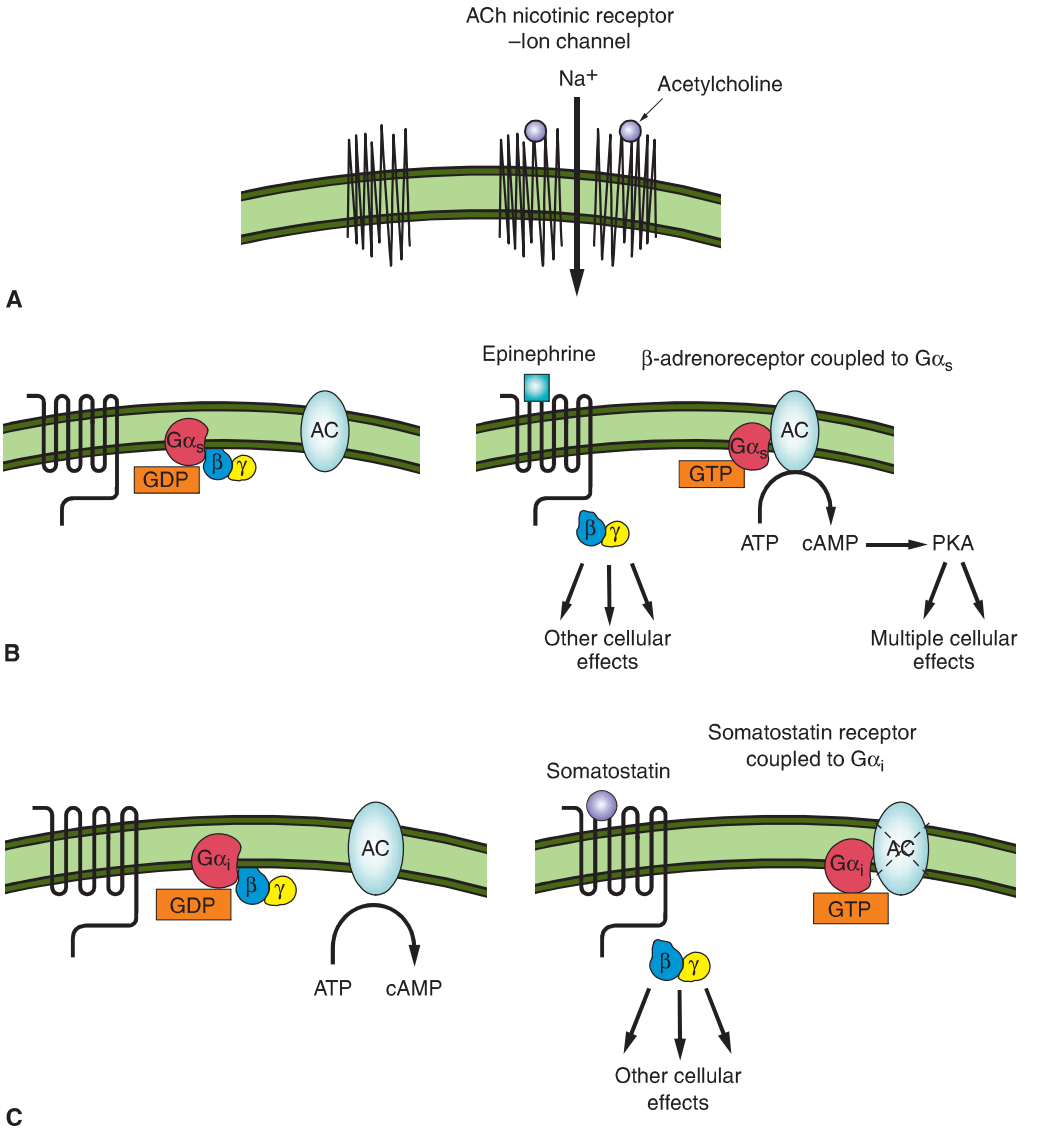
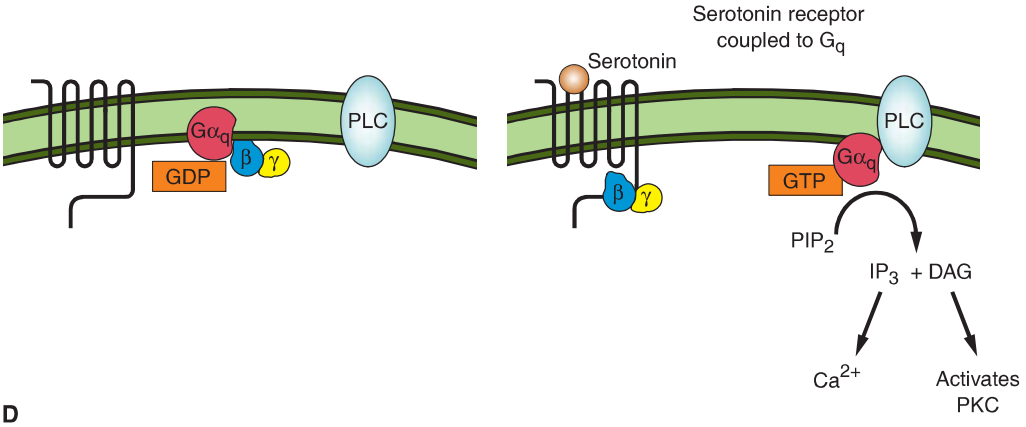


FIGURE 1.1. Four major classes of drug–receptor interactions, with specific examples of endogenous ligands. **A.** Acetylcholine interaction with a nicotinic receptor, a ligand-activated ion channel. **B–D.** G-protein–coupled receptors. **B.** Epinephrine interaction with a $G\alpha_s$-coupled β-adrenoceptor. **C.** Somatostatin interaction with a $G\alpha_i$ ($G\alpha_{inhibitory}$)-coupled receptor. **D.** Serotonin interaction with a G_q (and G_{11})-coupled receptor. **E.** Insulin interaction with a receptor-activated tyrosine kinase. **F.** Cortisol interaction with an intracellular nuclear receptor.



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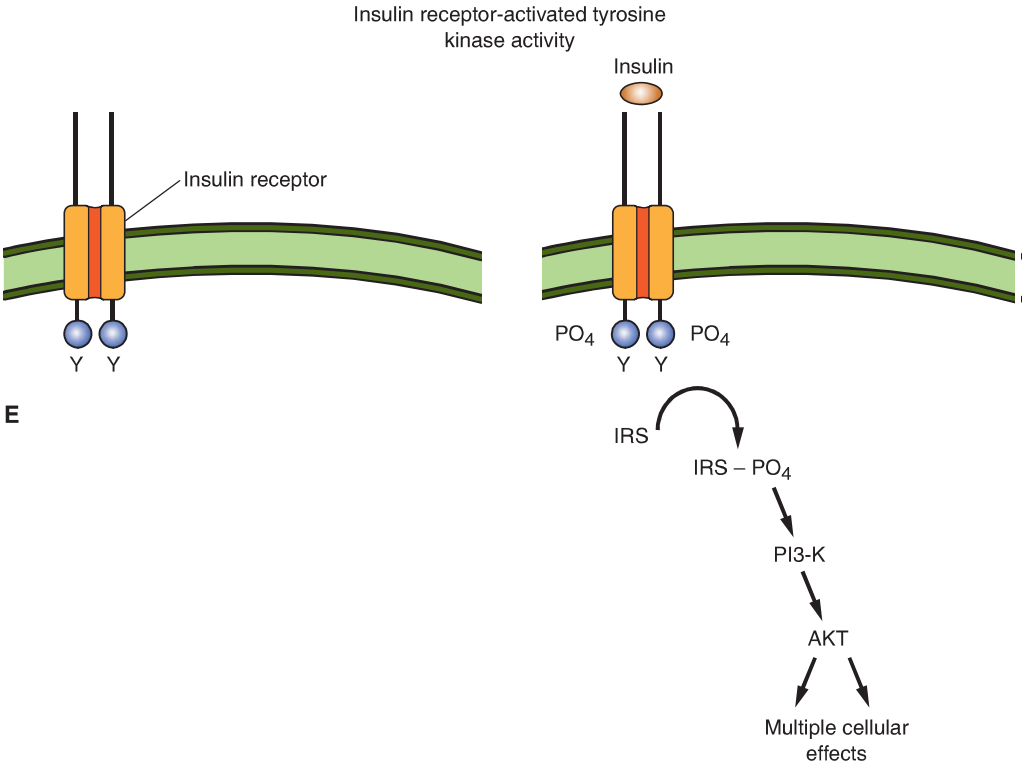


E

FIGURE 1.1. (*continued*)

2. ***Alteration of the activity of enzymes*** by activation or inhibition of the enzyme's catalytic activity.
3. ***Antimetabolite action***, in which the drug, acting as a nonfunctional analog of a naturally occurring metabolite, interferes with normal metabolism.
4. ***Nonspecific chemical or physical interactions***, such as those caused by antacids, osmotic agents, or chelators.

B. The graded dose–response curve. The graded dose–response curve expresses an individual's response to increasing doses of a given drug. The magnitude of a pharmacologic response is proportional to the number of receptors with which a drug effectively interacts (Fig. 1.2). The graded dose–response curve includes the following parameters:

1. ***Magnitude of response*** is graded; it continuously increases with the dose up to the maximal capacity of the system and is often depicted as a function of the logarithm of the dose administered (to see the relationship over a wide range of doses).

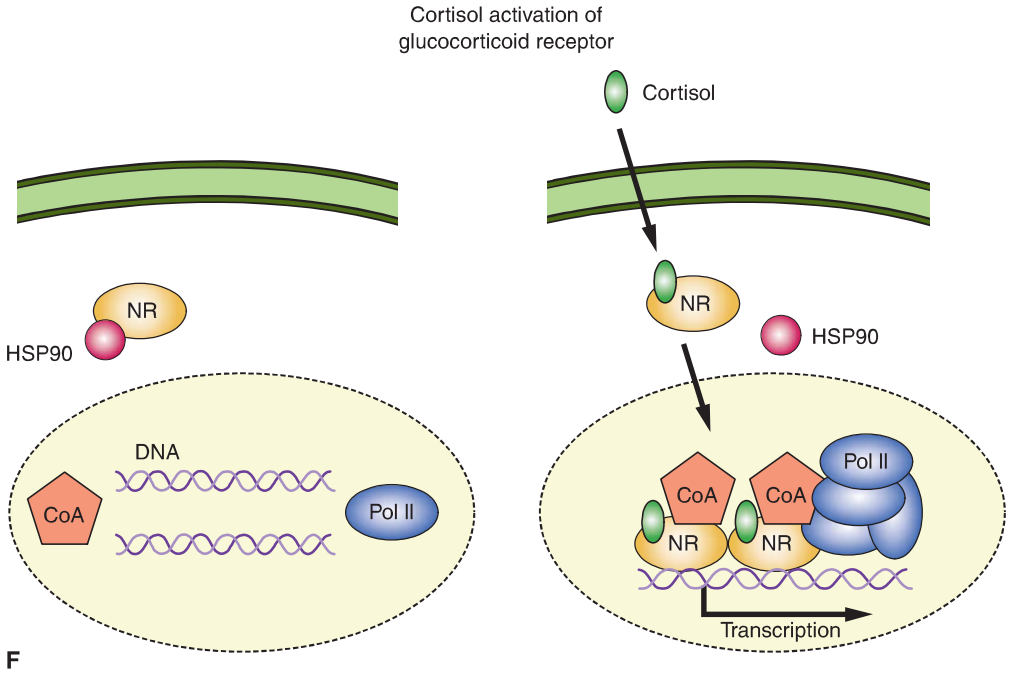


FIGURE 1.1. (*continued*)

2. ***Median effective dose (ED_{50})*** is the dose that produces the half-maximal response; the threshold dose is that which produces the first noticeable effect.
3. ***Intrinsic activity*** is the ability of a drug, once bound, to activate the receptor.
   - **a. Agonists** are drugs capable of binding to, and activating, a receptor.
     - **(1) Full agonists** occupy receptors to cause maximal activation.
       - **(a)** Intrinsic activity = 1
     - **(2) Partial agonists** can occupy receptors but cannot elicit a maximal response.
       - **(a)** Intrinsic activity of <1 (Fig. 1.3; drug C)
   - **b. Antagonists** bind to the receptor but do not initiate a response; they block the action of an agonist or endogenous substance that works through the receptor.
     - **(1) Competitive antagonists** combine with the same site on the receptor but their binding does not activate the receptor.

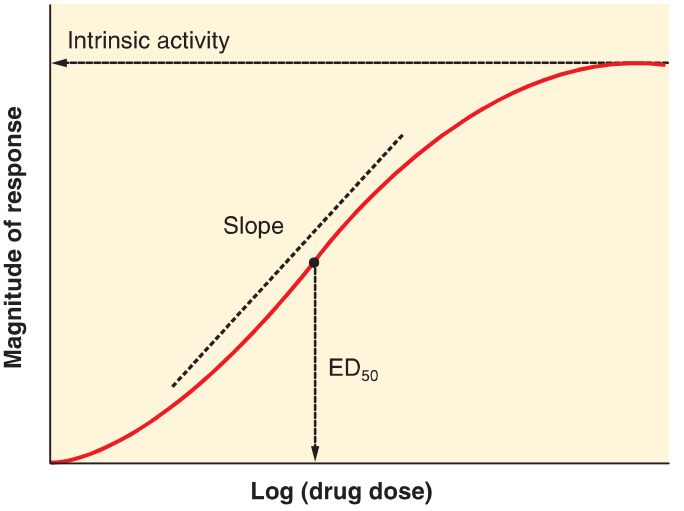


FIGURE 1.2. Graded dose–response curve.

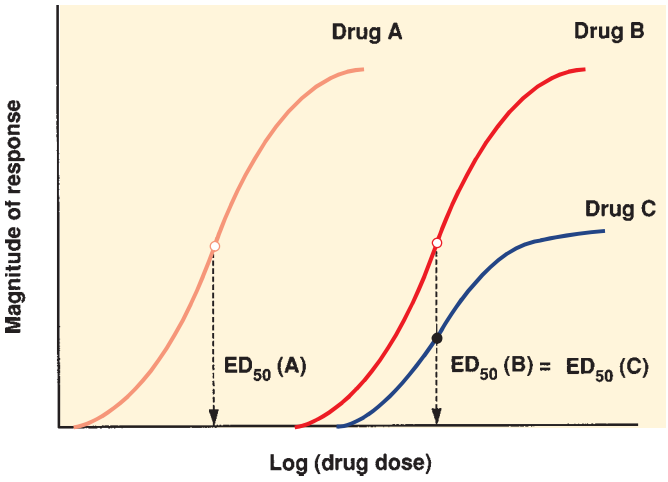


FIGURE 1.3. Graded dose–response curves for two agonists (**A** and **B**) and a partial agonist (**C**).

(a) Intrinsic activity = 0
(b) They may inhibit the actions of endogenous substances or other drugs.
(c) Competitive antagonists may be reversible or irreversible.
i. Reversible, or equilibrium, competitive antagonists are not covalently bound. They shift the dose–response curve for the agonist to the right and increase the ED_{50}, in which more agonist is required to elicit a response in the presence of the antagonist (Fig. 1.4). Because higher doses of agonist can overcome the inhibition, the maximal response can still be obtained.

(2) Noncompetitive antagonists bind to the receptor at a site other than the agonist-binding site (Fig. 1.5) and either prevent the agonist from binding correctly or prevent it from activating the receptor. Consequently, the effective amount of receptor is reduced. Receptors unoccupied by antagonist retain the same affinity for agonist, and the ED_{50} is unchanged.

4. ***Potency of a drug*** is the relative measure of the amount of a drug required to produce a specified level of response (e.g., 50%) compared with other drugs that produce the same effect via the same receptor mechanism.
   a. The potency of a drug is determined by the **affinity** of a drug for its receptor and the amount of administered drug that reaches the receptor site.
   b. The relative potency of a drug can be demonstrated by comparing the ED_{50} values of two full agonists; the drug with the lower ED_{50} is more potent (e.g., in Fig. 1.3, drug A is more potent than drug B).
5. ***The efficacy of a drug*** is the ability of a drug to elicit the pharmacologic response.
   a. Efficacy may be affected by such factors as the number of drug–receptor complexes formed, the ability of the drug to activate the receptor once it is bound (i.e., the drug's intrinsic activity), and the status of the target organ or cell.

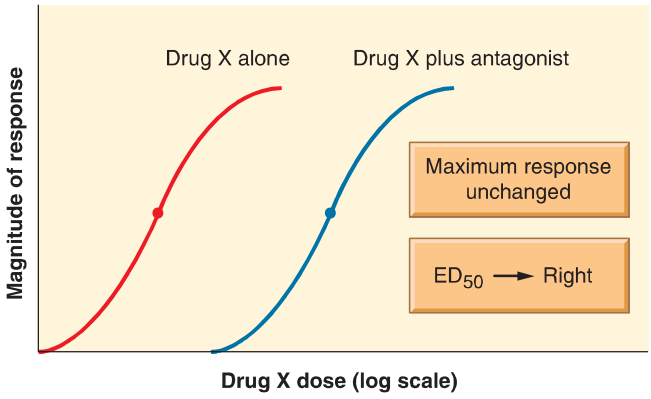


FIGURE 1.4. Graded dose–response curves illustrating the effects of competitive antagonists.

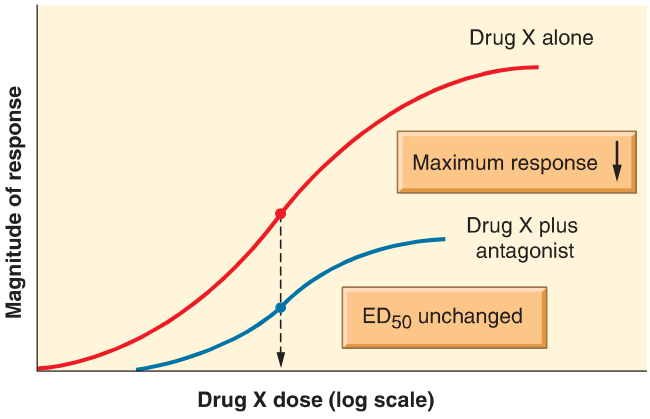


FIGURE 1.5. Graded dose–response curves illustrating the effects of non-competitive antagonists.

6. ***Slope*** is measured at the mid-portion of the dose–response curve.
   a. The slope varies for different drugs and different responses.
   b. Steep dose–response curves indicate that a small change in dose produces a large change in response.
7. ***Variability*** reflects the differences between individuals in response to a given drug.
8. ***Therapeutic index (TI)*** relates the desired therapeutic effect to undesired toxicity; it is determined using data provided by the quantal dose–response curve.
   a. The TI is defined as TD_{50}/ED_{50} (i.e., the ratio of the dose that produces a toxic effect in half of the population to the dose that produces the desired effect in half of the population).
   b. Note that the TI should be used with caution in instances when the quantal dose–response curves for the desired and toxic effects are not parallel.
   c. The **therapeutic range** (therapeutic window) is the serum concentration of drug required to **achieve therapeutic effects without toxicity**.
      (1) Serum concentrations for drugs with a **narrow therapeutic range** must be monitored closely; **small changes** in dose or organ dysfunction may lead to **therapeutic failure or toxicity**.

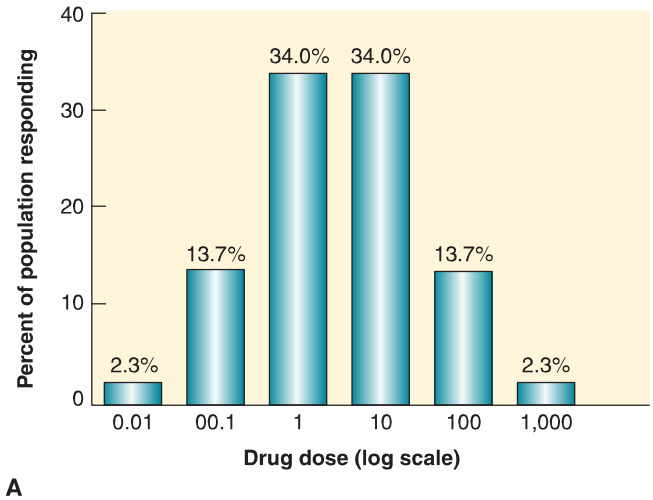
C. The quantal dose–response curve

1. The quantal dose–response curve (Fig. 1.6A and B) relates the dosage of a drug to the frequency with which a designated response will occur within a population.
   a. The response may be an "all-or-none" phenomenon (e.g., individuals either do or do not fall asleep after receiving a sedative) or a predetermined intensity of effect.
2. It is obtained via transformation of the data used for a frequency distribution plot to reflect the cumulative frequency of a response.
3. In the context of the quantal dose–response curve, ED_{50} indicates the dose of a drug that produces the response in half of the population. (Note that this differs from the meaning of ED_{50} in a graded dose–response curve.)
   a. For example, in Figure 1.6B, the ED_{50} would be 1. The TD_{50} for a drug would be determined from the midpoint of a similar curve indicating the cumulative percent of the population showing a toxic response to a drug.

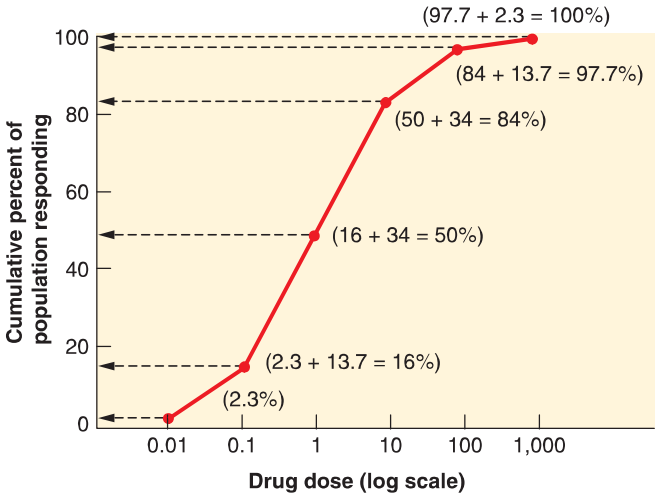
II. PHARMACOKINETICS AND PHARMACODYNAMICS

A. Pharmacokinetics. Pharmacokinetics is concerned with the **effect of the body on drugs**, or the movement of drugs throughout the body, including absorption, distribution, metabolism, and elimination.

B. Pharmacodynamics. Pharmacodynamics is concerned with the **effect of drugs on the body**, including the physiologic and molecular effects.



A



B

FIGURE 1.6. A. Frequency distribution plot. Number of individuals (as percentage of the population) who require the indicated drug dose to exhibit an identical response. As illustrated, 2.3% of the population require 0.01 units to exhibit the response, 13.7% require 0.1 units, and so on. **B.** Quantal dose–response curve. The cumulative number of individuals (as a percentage of the population) who will respond if the indicated dose of drug is administered to the entire population.

III. DRUG ABSORPTION

Drug absorption is the movement of a drug from its site of administration into the bloodstream. In many cases, a drug must be transported across one or more biologic membranes to reach the bloodstream.

A. Drug transport across membranes

1. ***Diffusion of unionized drugs*** is the most common and most important mode of traversing biologic membranes.
   - **a.** Drugs diffuse passively down their concentration gradient.
   - **b.** Diffusion can be influenced significantly by the **lipid–water partition coefficient** of the drug, which is the ratio of solubility in an organic solvent to solubility in an aqueous solution.
     (1) In general, **absorption increases as lipid solubility (partition coefficient) increases.**
   - **c.** Other factors that can also influence diffusion include the concentration gradient of the drug across the cell membrane and the surface area of the cell membrane.
2. ***Diffusion of drugs that are weak electrolytes***
   - **a.** Only the **unionized** form of a drug **can diffuse** to any significant degree across biologic membranes.

b. The degree of ionization of a weak acid or base is determined by the **pK of the drug and pH of its environment** according to the **Henderson-Hasselbalch equation**.

(1) For a weak acid (A):

$$HA \rightleftarrows H^+ + A^-,$$
$$pH = pK + \log[A^-]/[HA], \text{ and}$$
$$\log[A^-]/[HA] = pH - pK$$

where HA is the concentration of the protonated, or unionized, form of the acid and A^- is the concentration of the ionized, or unprotonated, form.

(2) For a weak base (B):

$$BH^+ \rightleftarrows H^+ + B,$$
$$pH = pK + \log[B]/[BH^+], \text{ and}$$
$$\log[B]/[BH^+] = pH - pK$$

where BH^+ is the concentration of the protonated form of the base and B is the concentration of the unprotonated form.

c. When the pK of a drug equals the pH of the surroundings, 50% ionization occurs, in which equal numbers of ionized and unionized species are present.

(1) A lower pK reflects a stronger acid.

(2) A higher pK corresponds to a stronger base.

d. Drugs with different pK values will diffuse across membranes at different rates.

e. The pH of the biologic fluid in which the drug is dissolved affects the degree of ionization and, therefore, the rate of drug transport.

f. **Ion trapping** occurs when a drug that is a weak acid or weak base **moves between fluid compartments with different pHs**; for example, when an oral drug is absorbed from the stomach (pH of 1–2) to plasma (pH of 7.4).

(1) The drug will tend to **accumulate** in the fluid compartment in which it is most **highly ionized**.

(a) Weak acids tend to accumulate in the fluid with the higher pH.

(b) Weak bases tend to accumulate in the fluid with the lower pH.

3. ***Active transport*** is an energy-dependent process that can move drugs against a concentration gradient through **protein-mediated transport systems**.

a. Active transport occurs in only one direction and is saturable.

b. It is usually the mode of transport for drugs that resemble actively transported endogenous substances such as sugars, amino acids, and nucleosides.

c. Some transport systems increase drug transport and entry into cells to increase drug effects. Others cause active efflux of drugs from target cells and decrease their activity.

4. ***Filtration*** is the bulk flow of solvent and solute through channels in the membrane.

a. It is seen with small molecules (usually with a molecular weight <100 Dalton [Da]) that can pass through the channels (pores).

b. Some substances with a greater molecular weight, like certain proteins, can be filtered through intercellular channels.

c. Concentration gradients affect the rate of filtration.

5. ***Facilitated diffusion*** is movement of a substance down a concentration gradient.

a. It is carrier mediated, specific, and saturable; it does not require energy.

B. Routes of administration

1. ***Oral administration***

a. **Sites of absorption**

(1) **Stomach**

(a) **Lipid-soluble drugs** and **weak acids**, which are normally unionized at the low pH of gastric contents, may be absorbed directly from the stomach.

(b) **Weak bases** and **strong acids** (pK = 2–3) are not normally absorbed from this site since they tend to exist as ions that carry either a positive or negative charge, respectively.

(2) **Small intestine**

(a) The small intestine is the **primary site of absorption** of most drugs because of the very large surface area across which drugs, including partially ionized weak acids and bases, may diffuse.

(b) Acids are normally absorbed more extensively from the small intestine than from the stomach, even though the intestine has a higher pH of 5–7.

b. The **bioavailability of a drug** is the fraction of drug (administered by any route) that reaches the bloodstream unaltered (bioavailability = 1 for intravenous administration). Bioequivalence refers to the condition in which the plasma concentrations versus time profiles of two drug formulations are identical.

(1) The **first-pass effect** influences drug absorption by metabolism in the liver or by biliary secretion. After absorption from the stomach or small intestine, a drug must pass through the liver before reaching the general circulation and its target site.

(a) If the capacity of liver metabolic enzymes to inactivate the drug is great, only limited amounts of active drug will escape the process.

i. During the first pass, the liver metabolizes some drugs so extensively that it precludes their use.

(2) Other factors that may alter absorption from the stomach or small intestine include the following:

(a) Gastric emptying time and passage of drug to the intestine may be influenced by **gastric contents** and **intestinal motility**.

i. A **decreased emptying time** generally **decreases the rate of absorption** because the intestine is the major absorptive site for most orally administered drugs.

(b) **Gastrointestinal (GI) blood flow** plays an important role in drug absorption by continuously maintaining the concentration gradient across epithelial membranes.

i. The absorption of small, very lipid-soluble molecules is "blood flow limited," whereas highly polar molecules are "blood flow independent."

(c) **Stomach acid** and enzyme inactivation may destroy certain drugs. Enteric coating prevents breakdown of tablets by the acidic pH of the stomach.

(d) **Interactions** with food, drugs, and other constituents of the gastric milieu may influence absorption.

(e) **Inert ingredients** in oral preparations may alter absorption.

2. ***Parenteral administration*** includes three major routes: **intravenous (IV), intramuscular (IM)**, and **subcutaneous (SC)**. Parenteral administration generally results in more predictable bioavailability than oral administration.

a. With **IV** administration, the drug is injected directly into the bloodstream (100% bioavailable). It represents the most rapid means of introducing drugs into the body and is particularly useful in the treatment of emergencies.

b. After **IM** and **SC** administration, many drugs can enter the capillaries directly through pores between endothelial cells.

3. ***Other routes of administration***

a. **Inhalation** results in **rapid absorption** because of the large surface area and rich blood supply of the alveoli.

(1) It is frequently used for gaseous anesthetics and for other drugs that act on the airways, such as the glucocorticoids used to treat bronchial asthma.

b. **Sublingual administration** is useful for drugs with **high first-pass metabolism**, since hepatic metabolism is bypassed.

c. **Intrathecal administration** is useful for drugs that do not readily cross the blood–brain barrier.

d. **Rectal administration** minimizes first-pass metabolism. It may be useful when oral drugs cannot be taken due to nausea and vomiting,

e. **Topical administration** is used widely when a local effect is desired or to **minimize systemic effects**, especially in dermatology and ophthalmology.

IV. DRUG DISTRIBUTION

Drug distribution is the movement of a drug from the bloodstream to the various tissues of the body.

A. Distribution of drugs. Distribution of drugs is the process by which a drug leaves the bloodstream and enters the extracellular fluids and tissues. A drug must diffuse across cellular membranes if its site of action is intracellular. In this case, lipid solubility is important for effective distribution.

1. ***Importance of blood flow***
   - **a.** In most tissues, drugs can leave the circulation readily by diffusion across or between capillary endothelial cells. Thus, the **initial rate of distribution** of a drug **depends heavily on blood flow** to various organs (brain, liver, kidney > muscle, skin > fat, bone).
   - **b.** At **equilibrium**, or **steady state**, the amount of drug in an organ is related to the mass of the organ and its properties, as well as the properties of the specific drug.
2. ***Volume of distribution (V_d)*** is the **volume of total body fluid** into which a drug appears to distribute after it reaches equilibrium in the body. Volume of distribution is determined by administering a known dose of drug (expressed in units of mass) intravenously and measuring the initial plasma concentration (expressed in units of mass/volume):

   $$V_d = \text{amount of drug administered (mg)} / \text{initial plasma concentration (mg/L)}$$

   Volume of distribution is expressed in units of volume. In most cases, the initial plasma concentration, C_0, is determined by extrapolation from the elimination phase.
   - **a. Standard values** of volumes of fluid compartments in an average 70-kilogram (kg) adult are as follows: plasma = 3 Liters (L); extracellular fluid = 12 L; and total body water = 41 L.
   - **b. Features** of volume of distribution.
     - **(1)** The use of V_d values is primarily conceptual, in which **drugs that distribute extensively have relatively large V_d values** and vice versa.
       - **(a)** A low V_d value may indicate extensive plasma protein binding of the drug.
       - **(b)** A high V_d may indicate that the drug is extensively bound to tissue sites.
     - **(2)** Among other variables, V_d may be influenced by age, sex, weight, and disease processes (e.g., edema, ascites).
3. ***Drug redistribution*** describes when the relative distribution of a drug in different tissues or fluid compartments of the body changes with time. This is usually seen with highly lipophilic drugs, such as thiopental, that initially enter tissues with high blood flow (e.g., the brain) and then quickly redistribute to tissues with lower blood flow (e.g., skeletal muscle and adipose tissue).
4. ***Barriers to drug distribution***
   - **a.** Blood–brain barrier
     - **(1)** **Ionized** or **polar drugs distribute poorly to the CNS**, because they must pass through, rather than between, endothelial cells.
     - **(2)** **Inflammation**, such as that resulting from meningitis, may increase the ability of ionized, poorly soluble drugs to cross the blood–brain barrier.
     - **(3)** The blood–brain barrier may not be fully developed at the time of birth.
   - **b.** Placental barrier
     - **(1)** **Lipid-soluble drugs** cross the placental barrier more easily than polar drugs.
     - **(2)** Drugs with a molecular weight of <600 Da pass the placental barrier more readily than larger molecules.
     - **(3)** The possibility that drugs administered to the mother may cross the placenta and reach the fetus is always an important consideration in therapy.

B. Binding of drugs by plasma proteins

1. Drugs in the plasma may exist in the free form or may be bound to plasma proteins or other blood components, such as red blood cells.
2. ***General features of plasma protein binding***
   - **a.** The extent of plasma protein binding is **highly variable**; depending on the drug, it may range from 0% to more than 99% bound. Binding is generally reversible.

b. Only free drug is small enough to pass through the spaces between the endothelial cells that form the capillaries; extensive binding slows the rate at which the drug reaches its site of action and may prolong duration of action.

c. Some plasma proteins bind many different drugs, whereas other proteins bind only one or a limited number. For example, **serum albumin tends to bind many acidic drugs**, whereas α_1-acid glycoprotein tends to bind many basic drugs.

V. METABOLISM (BIOTRANSFORMATION) OF DRUGS

A. General properties

1. Most drugs undergo biotransformation, or metabolism, after they enter the body.

a. It almost always produces metabolites that are more polar than the parent drug, often terminating the pharmacologic action and increasing removal of the drug from the body (via excretion).

b. **Metabolites carry ionizable groups** and are often **more charged and more polar** than the parent compounds.

(1) This increased charge may lead to a more rapid rate of clearance because of possible secretion by acid or base carriers in the kidney; it may also lead to decreased tubular reabsorption.

c. Possible consequences of biotransformation include the production of the following:

(1) **Inactive metabolites** (most common)

(2) Metabolites with increased or decreased potencies

(a) The active parent drugs may be metabolized to active metabolites.

(b) **Prodrugs** are inactive compounds that are metabolized to active drugs.

(3) Metabolites with qualitatively different pharmacologic actions

(4) Toxic metabolites

2. Many drugs undergo several sequential biotransformation reactions, which are catalyzed by specific enzyme systems.

3. The **liver is the major site of metabolism**, although specific drugs may undergo biotransformation in other tissues.

4. Drug metabolism can be affected by many parameters, including the following:

a. **Drugs** (drug–drug interactions) and **diet** (food–drug interactions)

b. Organ function and various disease states

(1) **Decreased liver function** may lead to decreased metabolism of certain drugs.

(2) Drug metabolism may decrease in cardiac and pulmonary disease.

c. **Age** and **developmental status**

(1) Very young children and elderly individuals may be more sensitive to drugs due to undeveloped or decreased levels of drug-metabolizing enzymes.

(2) Hormonal status and genetics may also affect drug metabolism.

B. Classification of biotransformation reactions

1. ***Phase I (nonsynthetic) reactions*** involve enzyme-catalyzed biotransformation of the drug without any conjugations.

a. They often convert the parent drug to a more polar (water soluble) compound.

(1) They frequently introduce a **polar functional group, such as —OH, —SH, or —NH_2,** which serves as the active center for sequential conjugation in phase II reactions.

(2) These include **oxidations, reductions**, and **hydrolysis reactions.**

b. Although phase I products may be excreted, in many cases, they undergo phase II reactions.

c. Enzymes catalyzing phase I include **cytochrome P-450**, aldehyde and alcohol dehydrogenase, deaminases, esterases, amidases, and epoxide hydratases.

2. ***Phase II (synthetic) reactions*** include **conjugation reactions**, which involve the enzyme-catalyzed combination of a drug with an endogenous substance.

a. The polar functional group of phase I products is often combined with glucuronic acid (**glucuronidation**), acetic acid (**acetylation**), or sulfuric acid (sulfation).

b. The final product is a highly polar conjugate that can be readily eliminated.

c. Enzymes catalyzing phase II biotransformation reactions include glucuronyl transferase (glucuronide conjugation), sulfotransferase (sulfate conjugation), transacylases (amino acid conjugation), acetylases, ethylases, methylases, and glutathione transferase.

C. Cytochrome P-450 monooxygenase (mixed function oxidase)

1. General features

a. Cytochrome P-450 monooxygenase plays a central role in drug biotransformation.

(1) This enzyme system is the one most frequently involved in **phase I reactions**.

(2) It catalyzes numerous reactions, including aromatic and aliphatic hydroxylations; dealkylation at nitrogen, sulfur, and oxygen atoms; heteroatom oxidations at nitrogen and sulfur atoms; reductions at nitrogen atoms; and ester and amide hydrolysis.

b. There are many types of cytochrome P-450 (CYP) enzymes.

c. Each type catalyzes the biotransformation of a unique spectrum of drugs, although there is some overlap with substrate specificities. The CYP families are referred to using Arabic numerals (e.g., CYP1, CYP2, etc.).

(1) Each family has a number of subfamilies denoted by an upper case letter (e.g., CYP2A, CYP2B, etc.).

(2) The individual enzymes within each subfamily are denoted by another Arabic numeral (e.g., CYP3A1, CYP3A2, etc.).

d. The **CYP2C, CYP2D, and CYP3A** enzymes are responsible for the metabolism of most drugs.

(1) **CYP3A4 is the most abundant hepatic enzyme** and is involved in the metabolism of over half of clinically important drugs.

2. The **primary location** of cytochrome P-450 is the **liver**, although significant levels are also found in the small and large intestine.

a. P-450 activity is also found in many other tissues, including the adrenals, ovaries and testis, and tissues involved in steroidogenesis and steroid metabolism.

b. The enzyme's subcellular location is the **endoplasmic reticulum**.

c. Lipid membrane location facilitates the metabolism of lipid-soluble drugs.

3. Mechanism of reaction

a. In the overall reaction, the drug is oxidized and oxygen is reduced to water.

b. Reducing equivalents are provided by **nicotinamide adenine dinucleotide phosphate (NADPH)**, and generation of this cofactor is coupled to **cytochrome P-450 reductase**.

c. The overall reaction for aromatic hydroxylation can be described as

$$\text{Drug} + O_2 + \text{NADPH} + H^+ \rightarrow \text{Drug} - \text{OH} + \text{NADP}^+ + H_2O$$

4. **Genetic polymorphism** of several clinically important cytochrome P-450s, particularly **CYP2C** and **CYP2D**, is a source of variable metabolism in humans, including differences among racial and ethnic groups. These enzymes have substantially different properties (V_{max} or K_m).

5. Induction

a. Enzyme induction may occur due to **drugs** and **endogenous substances**, such as hormones; they can preferentially induce one or more forms of CYP-450.

b. When caused by drugs, induction is pharmacologically important as a major source of **drug interactions**. A drug may induce its own metabolism (metabolic tolerance) or that of other drugs.

(1) Induction can be caused by a wide variety of drugs, such as quinidine, phenytoin, **phenobarbital, rifampin,** and **carbamazepine.**

(2) Environmental agents, such as **tobacco smoke**, may also induce CYP-450 enzymes.

c. Some of the same drugs that induce CYP3A4 can induce the drug efflux transporter P-glycoprotein, such as rifampin and St. John's wort.

6. Inhibition

a. Competitive or noncompetitive (clinically more likely) inhibition of P-450 enzyme activity can result in the **reduced metabolism of other drugs** or endogenous substrates, such as **testosterone**.

b. Enzyme inhibition is a **major source of drug–drug interactions**. It is caused by a number of commonly used drugs, including **cimetidine, fluconazole, fluoxetine**, and **erythromycin. Environmental or dietary agents (e.g., grapefruit juice**) can also cause enzyme inhibition.

c. Some of the same drugs that inhibit CYP3A4 can inhibit the drug efflux transporter P-glycoprotein, including amiodarone, clarithromycin, erythromycin, and ketoconazole.

D. Glucuronyl transferase

1. General features
   a. Glucuronyl transferase is a set of enzymes with unique, but overlapping, specificities that are involved in **phase II reactions**.
   b. It catalyzes the conjugation of glucuronic acid to a variety of active centers, including —OH, —COOH, —SH, and —NH_2.
2. Location and induction
   a. Glucuronyl transferase is located in the **endoplasmic reticulum**.
   b. It is the only phase II reaction that is **inducible by drugs** and is a possible site of drug interactions.

E. Hepatic extraction of drugs

1. General extraction by the liver occurs because of the liver's large size (1,500 g) and high blood flow (1 mL/g/min).
2. The **extraction ratio** is the amount of drug removed in the liver divided by the amount of drug entering the organ; a drug completely extracted by the liver would have an extraction ratio of 1. Highly extracted drugs can have a hepatic clearance approaching 1,500 mL/min.
3. **First-pass effect.** Drugs taken orally pass across membranes of the GI tract into the portal vein and through the liver before entering the general circulation.
   a. **Bioavailability** of orally administered drugs is **decreased** by the fraction of drug removed by the first pass through the liver. For example, a drug with a hepatic extraction ratio of 1 would have 0% bioavailability; a drug such as lidocaine, with an extraction ratio of 0.7, would have 30% bioavailability.
   b. In the presence of hepatic disease, drugs with a high first-pass extraction may reach the systemic circulation in higher than normal amounts, and dose adjustment may be required.

VI. DRUG ELIMINATION AND TERMINATION OF ACTION

A. Mechanisms of drug elimination and termination of action

1. In most cases, the action of a drug is terminated by **enzyme-catalyzed conversion** to an inactive (or less active) compound and/or **elimination from the body** via the kidney or other routes.
2. Redistribution of drugs from the site of action may terminate the action of a drug, although this occurs infrequently. For example, the action of the anesthetic **thiopental** is terminated largely by its redistribution from the brain (where it initially accumulates as a result of its high lipid solubility and the high blood flow to that organ) to the more poorly perfused adipose tissue.

B. Routes of excretion

1. Routes of excretion may include urine, feces (e.g., unabsorbed drugs and drugs secreted in bile), saliva, sweat, tears, milk (with possible transfer to neonates), and lungs (e.g., alcohols and anesthetics).
2. Any route may be important for a given drug, but the **kidney is the major site of excretion** for most drugs.
3. Some drugs are secreted by liver cells into the bile, pass into the intestine, and are eliminated in the feces (e.g., rifampin, indomethacin, estradiol).
4. Some drugs undergo **enterohepatic circulation** (reabsorbed from the intestine); in this case, the drug effect may be prolonged.

C. General principles for drug clearance (CL)

1. Conceptually, clearance is a measure of the capacity of the body to remove a drug.
2. Mathematically, clearance is the proportionality constant that relates the rate of drug elimination to the plasma concentration of the drug.
   a. The units of clearance are volume/time.
   b. Drugs with high clearance are rapidly removed from the body.
   c. Drugs with low clearance are removed slowly from the body.

3. ***Specific organ clearance*** is the capacity of an individual organ to eliminate a drug. It may be due to metabolism (e.g., hepatic clearance by the liver) or excretion (e.g., renal clearance by elimination in the urine).

$$\text{Rate of elimination by organ} = CL_{organ} \times [Drug]_{plasma\ perfusing\ organ}$$

or

$$CL_{organ} = \text{Rate of elimination by organ}/[Drug]_{plasma\ perfusing\ organ}$$

4. ***Whole body clearance*** is the capacity of the body to eliminate the drug by all mechanisms. Therefore, whole body clearance is equal to the sum of all of the specific organ clearance mechanisms by which the active drug is eliminated from the body:

$$CL_{whole\ body} = CL_{organ\ 1} + CL_{organ\ 2} + CL_{organ\ N}$$

The term "clearance" generally refers to whole body clearance unless otherwise specified. In this case,

$$\text{Rate of elimination from body} = CL_{whole\ body} \times [Drug]_{plasma}$$

and

$$CL = \text{Rate of elimination from body}/[Drug]_{plasma}$$

5. ***Plasma clearance*** is numerically the same as whole body clearance, but this terminology is sometimes used because clearance may be viewed as the volume of plasma that contains the amount of drug removed per unit time (recall that the units of clearance are volume/time).
   - **a.** If not specified, this term refers to the volume of plasma "cleared" of drug by all bodily mechanisms (i.e., whole body clearance).
   - **b.** The term may also be applied to clearance by specific organs; for example, renal plasma clearance is the volume of plasma containing the amount of drug eliminated in the urine per unit time.

D. Net renal excretion of drugs

1. ***Net renal excretion*** of drugs is the result of **three separate processes:** (1) the amount of drug filtered at the glomerulus, (2) plus the amount of drug secreted by active transport mechanisms in the kidney (3) minus the amount of drug passively reabsorbed throughout the tubule.
   - **a. Filtration**
     - **(1)** Most drugs have low molecular weights and are freely filtered from the plasma at the glomerulus.
     - **(2)** Serum protein binding reduces filtration since plasma proteins are too large to be filtered.
     - **(3)** Compared to adults, the glomerular filtration rate (GFR) is 30%–40% lower during a child's first year of life.
   - **b. Secretion**
     - **(1)** The kidney proximal tubule contains **two transport systems** that may secrete drugs into the ultrafiltrate, one for **organic acids** (organic acid transporters or OATs) and a second for **organic bases** (organic base transporters or OBTs).
       - **(a)** There are multiple OATs and OBTs with specificities for different organic molecules in the tubule.
       - **(b)** They **require energy for active transport** against a concentration gradient.
       - **(c)** They are also a site for potential **drug–drug interactions;** drugs may compete with each other for binding to the transporters.
     - **(2)** Plasma protein binding does not normally have a large effect on secretion because the affinity of the transport systems for most drugs is greater than the affinity of plasma-binding proteins.
   - **c. Reabsorption**
     - **(1)** Reabsorption may occur throughout the tubule; some compounds, including endogenous compounds such as glucose, are actively reabsorbed.
     - **(2)** Reabsorption of the **unionized form** of drugs that are weak acids and bases can occur by simple **passive diffusion**, the rate of which depends on the lipid solubility and pK of the drug, as well as the concentration gradient of the drug between the urine and the plasma.

(3) Reabsorption may be affected by **alterations of urinary pH**, which affects elimination of weak acids or bases by altering their ionization (i.e., **ion trapping**).
(a) For example, alkalinization of the urine will result in a higher proportion of the ionized form of an acidic drug that will decrease its reabsorption and hence increase its elimination.

2. ***Renal clearance of drugs***
a. Renal clearance measures the volume of plasma that is cleared of drug per unit time:

$$CL\,(mL/min) = U \times V/P$$

where **U** is the concentration of drug per milliliter of **urine, V the volume** of the urine excreted per minute, and **P** the concentration of drug per milliliter of **plasma**.
(1) A drug excreted by **filtration alone** will have a clearance equal to the GFR (125–130 mL/min).
(2) A drug excreted by **filtration and complete secretion** will have a clearance equal to renal plasma clearance (650 mL/min).
(3) Clearance values between 130 and 650 mL/min suggest that a drug is **filtered, secreted, and partially reabsorbed**.
b. A variety of factors influence renal clearance, including age, other drugs, and disease.
c. In the presence of **renal failure**, the clearance of a drug may be reduced significantly, resulting in higher plasma levels (dose reductions may be required).

VII. PHARMACOKINETIC PRINCIPLES

A. General pharmacokinetic principles

1. Pharmacokinetics describes changes in plasma drug concentration over time.
2. Although it is ideal to determine the amount of drug that reaches its site of action as a function of time after administration, it is usually impractical or not feasible.
a. The plasma drug concentration is measured since the amount of drug in the tissues is generally related to plasma concentration.

B. Distribution and elimination

1. ***One-compartment model*** (Fig. 1.7)
a. The drug appears to distribute instantaneously after IV administration of a single dose. If the mechanisms for drug elimination, such as biotransformation by hepatic enzymes and renal secretion, are not saturated following the therapeutic dose, a semilog plot of plasma concentration versus time will be **linear**.

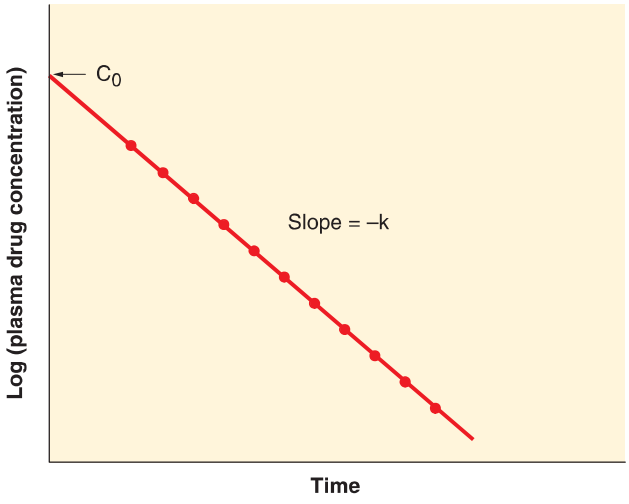


FIGURE 1.7. One-compartment model of drug distribution.

b. Drug elimination is **first order**, in which a **constant fraction** of drug is eliminated per unit time.
(1) For example, one-half (50%) of the drug is eliminated every 8 hours.
(2) Elimination of most drugs is a first-order process.

c. The slope of the semilog plot is **—k**, where **k is the rate constant of elimination** and has units of time and the intercept on the y axis is C_0. (*Note:* C_0 is used to calculate V_d for drugs that obey a one-compartment model.)

d. The **plasma drug concentration (C_t) relative to the initial concentration (C_0)** at any time (t) after administration is given by

$$\ln C_t = \ln C_0 - kt$$

and the **relationship of the plasma concentrations** at any two points in time is given by

$$\ln C_2 = \ln C_1 - k\,(t_2 - t_1)$$

2. ***Two-compartment model*** (Fig. 1.8)

a. The two-compartment model is a **more common model for distribution and elimination** of drugs.

b. **Initial rapid decreases in the plasma concentration** of a drug are observed because of a **distribution phase**, which is the time required for the drug to reach an **equilibrium** distribution between a central compartment, such as the plasma space, and a second compartment, such as the aggregate tissues and fluids to which the drug distributes.
(1) During this phase, plasma drug concentrations decrease very rapidly because the drug is being eliminated from the body (e.g., by metabolism and renal elimination), as well as exiting the plasma space as it distributes to other tissues and fluid compartments.

c. After distribution, a linear decrease in the log drug concentration is observed if the **elimination phase** is first order. The curve is less steep in this phase because there is no longer a net decrease in plasma levels of drug due to distribution to the tissues (which has been completed).

d. For drugs that obey a two-compartment model, the value of C_0 obtained by extrapolation of the elimination phase is used to calculate V_d, and the elimination rate constant, k, is obtained from the slope of the elimination phase.

e. The expressions for $\ln C_t$ and clearance (CL) shown above for a one-compartment model also apply during the elimination phase for drugs that obey a two-compartment model.

3. ***First-order elimination***

a. The elimination of **most drugs** at therapeutic doses is **first order**, where a **constant fraction of drug is eliminated per unit time**.
(1) It occurs when the drug does not saturate elimination systems.
(2) The rate of elimination is a **linear function** of the plasma drug concentration.

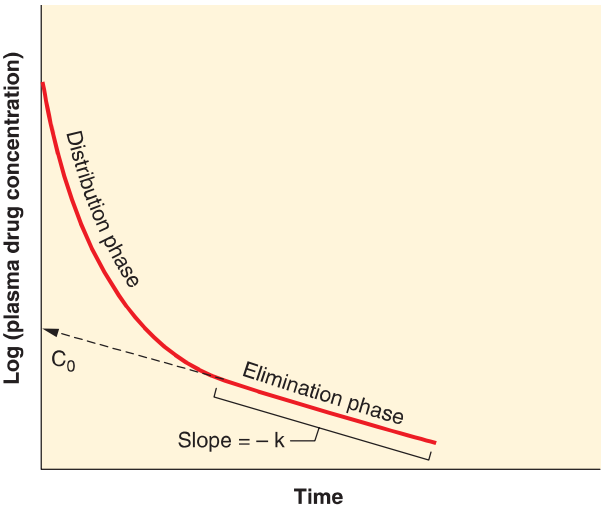


FIGURE 1.8. Two-compartment model of drug distribution.

b. The rate of elimination depends on the concentration of drug in the plasma and is equal to the plasma concentration of the drug multiplied by a **proportionality constant:**

$$\text{Rate of elimination from body (mass/time)} = \text{Constant} \times [\text{Drug}]_{\text{plasma}}\,\text{(mass/vol)}$$

Because the rate of elimination is given in units of mass/time and concentration is in units of mass/volume, the units of the constant are volume/time. This constant is referred to as the clearance of the drug.

4. ***Zero-order elimination***

a. **Zero-order** elimination occurs when a **constant amount of the drug is eliminated per unit time**; it does **not depend on plasma concentration**.

(1) It may occur when **therapeutic doses of drugs exceed the capacity of elimination mechanisms** (the mechanism by which the body eliminates the drug, such as hepatic metabolism or kidney secretion, is saturated).

b. In this model, the plot of the log of the plasma concentration versus time will decrease in a concave upward manner (e.g., 10 mg of drug will be eliminated every 8 h). (Note that after an interval of time sufficient to reduce the drug level below the saturation point, first-order elimination occurs.)

c. Examples of drugs removed by zero-order kinetics include phenytoin and ethanol.

C. Half-life ($t_{1/2}$)

1. Half-life is the time it takes for the **plasma drug concentration to be reduced by 50%**. This concept only applies to drugs eliminated by **first-order kinetics**.

2. Half-life is determined by the following:

a. Log plasma drug concentration versus time profile for drugs fitting a one-compartment model.

b. Elimination phase for drugs fitting the two-compartment model.

c. If the dose administered does not exceed the capacity of the elimination systems (i.e., the dose does not saturate those systems), the half-life will remain constant.

3. The half-life is related to the **elimination rate constant (k)** by the equation $\mathbf{t_{1/2} = 0.693/k}$ (i.e., for a steep decrease in concentration, k is high; therefore, $t_{1/2}$ is short).

4. It is related to the **volume of distribution (V_d)** and **clearance (CL)** by the equation $t_{1/2} = \mathbf{0.693\ V_d/CL}$.

a. This relationship emphasizes that drugs that are widely distributed in the body (i.e., a high V_d) will take longer to be eliminated and drugs for which the body has a high capacity to remove (i.e., a high CL) will take a short time to be eliminated.

5. In most cases, over 95% of the drug will be **eliminated in a time interval equal to five half-lives**; this applies for therapeutic doses of most drugs.

D. Multidose kinetics

1. ***Infusion and multidose repeat administration***

a. If a drug is given by continuous IV infusion at a constant dose rate and elimination is first order, it will eventually reach a constant steady-state plasma concentration.

(1) The **steady-state concentration** occurs when the **rate of elimination is equal to the rate of administration**.

b. If a drug that is eliminated by first-order kinetics is administered repeatedly (e.g., one tablet or injection every 8 h), the *average* plasma concentration of the drug will increase until a *mean* steady-state level is reached.

(1) This will not occur for drugs that exhibit zero-order elimination.

c. The **time required to reach steady state is equal to five half-lives** regardless of whether administration is via continuous infusion or repeated administration.

(1) Whenever a dose rate is changed, it will take five half-lives for a new steady-state level to be reached for any route of administration.

2. ***Steady state after repeat administration***

a. Some fluctuation in plasma concentration will occur even at steady state.

b. Levels will be at the high point of the steady-state range shortly after a dose is administered; levels will be at the low point immediately before administration of the next dose. Hence, **steady state designates an average plasma concentration** and the range of fluctuations above and below that level.

c. The magnitude of fluctuations can be controlled by the **dosing interval**.

(1) A shorter dosing interval decreases fluctuations, and a longer dosing interval increases them.

d. On cessation of multidose administration, over 95% of the drug will be eliminated in a time interval equal to five half-lives if first-order kinetics applies.

3. *Maintenance dose rate*

a. The **maintenance dose rate** is the dose of a drug required per unit time to **maintain a desired steady-state level** in the plasma to sustain a specific therapeutic effect.

b. To determine the dose rate required to maintain an average steady-state plasma concentration of drug, multiply the desired plasma concentration by the CL:

$$\text{Maintenance dose rate} = \text{Desired}\left[\text{drug}\right]_{\text{plasma}} \times \text{Clearance (CL)}$$
$$(\text{amount/time}) = (\text{amount/volume}) \times (\text{volume/time})$$

This yields dose rate in units of amount per time (e.g., mg/h).

(1) To remain at steady state, the **dose rate must equal the elimination rate.**

(a) The rate at which the drug is added to the body must equal the rate at which it is eliminated.

(2) The elimination rate = CL × $[\text{Drug}]_{\text{plasma}}$; therefore, because the dose rate must equal the elimination rate to be at steady state, dose rate also equals CL × Desired $[\text{drug}]_{\text{plasma}}$.

c. If the drug is administered at the maintenance dose rate, a steady-state plasma concentration will be reached in four to five half-lives. (*Note:* This is four to five half-lives, not four to five doses!)

4. *Loading dose*

a. For certain drugs, an initial loading dose may be given to achieve rapid levels and earlier therapeutic effects; this may be useful in potentially life-threatening situations, such as a severe infection (e.g., aminoglycosides, vancomycin) or pulmonary embolism (e.g., heparin).

b. To calculate the loading dose, the desired plasma concentration of drug can be multiplied by the V_d:

$$\text{Loading dose} = \text{Desired}\left[\text{drug}\right]_{\text{plasma}} \times V_d$$
$$(\text{amount or mass}) = (\text{mass/volume}) \times (\text{volume})$$

c. After administration of the loading dose (which rapidly achieves the desired plasma concentration of drug), the drug is administered at the maintenance dose rate to maintain the drug concentration at the desired steady-state level.

Review Test

Directions: Select the best answer for each question.

1. Somatostatin interacts with which of the following receptors?

(A) G_i-protein–coupled receptor
(B) G_q-protein–coupled receptor
(C) Intracellular nuclear receptor
(D) Ligand-activated ion channel
(E) Receptor-activated tyrosine kinase

2. What characteristic gives cortisol the ability to target intranuclear receptors?

(A) Diffuse through lipid membranes
(B) Interact with adenylyl cyclase
(C) Interact with G-protein–coupled receptors
(D) Recruit intracellular kinases
(E) Undergo autophosphorylation

3. A 66-year-old man is admitted to the hospital with confusion, nausea, and blurred vision. He is currently on digoxin for the treatment of heart failure. On physical exam, his heart rate is 120 bpm. Further evaluation reveals a digoxin level of 5.3 ng/mL (normal range: 0.5–2 ng/mL). The doctor believes his symptoms are due to digoxin toxicity. Which parameter is used to indicate the ability of digoxin to produce the desired effect relative to a toxic effect?

(A) Bioavailability
(B) Efficacy
(C) Intrinsic activity
(D) Potency
(E) Therapeutic index

4. A 64-year-old woman presents to the emergency room with severe abdominal pain and feculent emesis. She has a history of multiple abdominal surgeries due to Crohn disease. Further evaluation reveals a small bowel obstruction. A few hours later, she undergoes surgery for lysis of adhesions and resection of the small bowel. Why should the use of oral medications be avoided in this patient?

(A) Decreased passage of drug through intestine
(B) Decreased gastrointestinal blood flow
(C) Destruction of drug by stomach acid
(D) Increased first-pass effect
(E) Increased protein binding of the drug

5. An 82-year-old woman is admitted to the hospital for management of a heart failure exacerbation. She has peripheral edema and ascites due to the exacerbation. Further evaluation also reveals a urinary tract infection requiring antibiotic treatment. Due to her history of heart failure, changes in what pharmacodynamic parameter should be considered prior to choosing the most appropriate antibiotic dose?

(A) Impaired blood flow to the intestine
(B) Increased protein binding of various drugs
(C) Increased volume of distribution
(D) Increased drug elimination

6. Which of the following terms is used to describe the elimination rate via metabolism catalyzed by alcohol dehydrogenase when the enzyme is saturated?

(A) Biotransformation
(B) Clearance
(C) First-order elimination
(D) Redistribution
(E) Zero-order kinetics

7. Which of the following statements are true in regard to glucuronidation reactions?

(A) Considered phase I reactions
(B) Include the enzymatic activity of alcohol dehydrogenase
(C) Require an active center as the site of conjugation
(D) Require nicotinamide adenine dinucleotide phosphate

8. A 38-year-old woman presents to her psychiatrist for the management of depression. She feels that her current treatment is ineffective and would like to switch medications. The patient reveals that she drinks alcohol every night to relieve her feelings of sadness and guilt. Blood work is positive for elevated liver

enzymes. The doctor starts imipramine, which has an extensive first-pass metabolism. How would this drug be affected?

(A) Decreased half-life
(B) Decreased absorption
(C) Decreased solubility
(D) Increased concentration
(E) Increased pH

9. A 24-year-old female is prescribed erythromycin for gastroparesis. It is prescribed four times daily due to its short half-life. What is the rationale for such a frequent dosing?

(A) Achieve the steady-state plasma concentration of the drug
(B) Aid more complete distribution of the drug
(C) Avoid the toxicity of the drug because of its low therapeutic index
(D) Ensure that the drug concentration remains constant over time
(E) Inhibit the first-pass metabolism of the drug

10. A 78-year-old woman is started on digoxin for the management of congestive heart failure. Her initial dose is 0.25 mg. The C_0, obtained by extrapolation of the elimination phase, is determined to be 0.05 mg/L. What is the patient's estimated volume of distribution?

(A) 0.0125 L
(B) 0.2 L
(C) 0.5 L
(D) 1 L
(E) 5 L

11. A drug has a volume of distribution of 50 L. At plasma concentrations over 2 mg/L, it undergoes zero-order elimination at a rate of 2 mg/h. If a patient is brought to the emergency room with a plasma concentration of 4 mg/L of the drug, how long will it take (in hours) for the plasma concentration to decrease by 50%?

(A) 1
(B) 2
(C) 10
(D) 25
(E) 50

12. A 100-mg tablet of drug X is given to a patient every 24 hours to achieve an average steady-state plasma concentration of 10 mg/L. If the dosing regimen is changed to one 50 mg tablet every 12 hours, what will be the resulting average plasma concentration (in mg/L) of the drug after five half-lives?

(A) 2.5
(B) 5
(C) 10
(D) 20
(E) 40

13. A 35-year-old woman is started on ceftriaxone as empiric therapy for meningitis. Following intravenous administration, the initial rates of drug distribution to different tissues depend primarily on which of the following parameters?

(A) Active transport of the drug out of different cell types
(B) Blood flow to the tissues
(C) Degree of ionization of the drug in the tissues
(D) Fat content of the tissues
(E) Specific organ clearances

14. A drug is administered in the form of an inactive prodrug. The prodrug increases the expression of a cytochrome P-450, which converts it to its active form. With chronic, long-term administration of the prodrug, which of the following will be observed?

(A) Efficacy will decrease
(B) Efficacy will increase
(C) Potency will decrease
(D) Potency will increase

15. Which subfamily of cytochrome P-450s is responsible for the highest fraction of clinically important drug interactions resulting from metabolism?

(A) CYP1A
(B) CYP2A
(C) CYP3A
(D) CYP4A
(E) CYP5A

16. If the oral dosing rate of a drug is held constant, what will occur if the bioavailability is increased?

(A) Decreased first-order elimination rate constant
(B) Decreased total body clearance
(C) Increased half-life for first-order elimination
(D) Increased steady-state plasma concentration
(E) Increased volume of distribution

17. A 45-year-old man is given an oral maintenance dose of drug calculated to achieve a steady-state plasma concentration of 5 mcg/L.

After dosing the patient for a sufficient amount of time to reach steady state, the average plasma concentration of drug is 10 mcg/L. A decrease in which of the following parameters may explain the higher than anticipated plasma drug concentration?

(A) Bioavailability
(B) Clearance
(C) Half-life
(D) Volume of distribution

18. Administration of an intravenous loading dose of drug X yields an initial plasma concentration of 100 mcg/L. The table below illustrates the plasma concentration of drug X as a function of time after the initial loading dose.

Time (h)	Plasma Conc. (mcg/L)
0	100
1	50
5	25
9	12.5

What is the half-life (in h) of drug X?

(A) 1
(B) 2
(C) 4
(D) 5
(E) 9

19. Which of the following factors will determine the number of drug–receptor complexes formed?

(A) Half-life of the drug
(B) Rate of renal secretion
(C) Receptor affinity for the drug
(D) Therapeutic index of the drug

20. Which of the following is an action of a noncompetitive antagonist?

(A) Alters the mechanism of action of an agonist
(B) Alters the potency of an agonist
(C) Binds to the same site on the receptor as the agonist
(D) Decreases the maximum response to an agonist
(E) Shifts the dose–response curve of an agonist to the right

21. The renal clearance of a drug is 10 mL/min. The drug has a low molecular weight and is 20% bound to plasma proteins. It is most likely that renal excretion of this drug involves which of the following mechanisms?

(A) Active tubular secretion only
(B) Glomerular filtration only
(C) Glomerular filtration and active tubular secretion
(D) Glomerular filtration and passive tubular reabsorption
(E) Passive tubular reabsorption only

Answers and Explanations

1. **The answer is A.** Somatostatin binds to a G_i-coupled protein receptor, initiating exchange of GTP for GDP, which inhibits AC and leads to reduced cAMP production. The G_q-protein–coupled receptor is an example of the PLC pathway, in which interaction with the ligand leads to increased PLC activity and eventual activation of protein kinase C via the PIP_2 and IP_3 pathway. This is exemplified by interaction of epinephrine with its receptor. The ligand-activated ion channel is an example of interaction of specific ligand with an ion channel, which permits passage of ions through the channel. Acetylcholine is an example of such an interaction. Receptor-activated tyrosine kinase is exemplified by insulin, where binding of ligand activates specific tyrosine kinase, leading to a cascade of reactions within the cell. Finally, an intracellular nuclear receptor is exemplified by cortisol, which binds to it and exerts its effects on DNA replication.
2. **The answer is A.** The ability to target intracellular receptors depends on the ligand's ability to cross lipid barriers, such as the nuclear envelope. Recruitment of intracellular kinases is characterized by some receptor-activated tyrosine kinases. Autophosphorylation is a feature of many different kinases. Interactions with G-protein and AC are characteristics of membrane receptors.
3. **The answer is E.** Digoxin is an example of a drug with a very low therapeutic index (TI), which requires frequent monitoring of the plasma level to achieve the balance between the desired effect and untoward toxicity. Potency of the drug is the amount of drug needed to produce a given response. Intrinsic activity of the drug is the ability to elicit a response. Efficacy of the drug is the maximal drug effect that can be achieved in a patient under a given set of conditions. Bioavailability of the drug is the fraction of the drug that reaches the bloodstream unaltered.
4. **The answer is A.** Adequate passage of drug through the small intestine is required to observe the effects of the drug, because most of the absorption takes place in the small intestine. After extensive abdominal surgery, especially that involving a resection of a portion of small bowel, the passage may be slowed, or even stopped, for a period of time. Abdominal surgery rarely results in reduced blood flow to the intestine, nor does such an operation influence protein binding, or the first-pass effect. Destruction of drug by stomach acid does not depend on intra-abdominal surgery.
5. **The answer is C.** Because of the patient's edema and ascites from heart failure, the apparent volume of distribution will be increased, which may require small adjustments in the usual medication doses. Edematous states do not influence gastrointestinal (GI) blood flow, nor do they affect drug–protein interactions. Drug elimination may be slowed with a congestive heart failure (CHF) exacerbation, not increased. Drug kinetics are generally not changed by edematous states.
6. **The answer is E.** Alcohol (ethanol) is one of the few drugs that follow zero-order kinetics (i.e., higher drug concentrations are not metabolized because the enzyme that is involved in the process is saturable). In first-order elimination, the rate of elimination actually depends on the concentration of the drug, multiplied by the proportionality constant. Clearance is a measure of the capacity of the body to remove the drug. Biotransformation refers to the general mechanism of a particular drug's elimination. Redistribution is one of the possible fates of a drug, which usually terminates drug action.
7. **The answer is C.** Glucuronidation reactions, which are considered phase II reactions, require an active center (a functional group) as the site of conjugation. Phase I reactions are biotransformation reactions, not conjugation reactions. Alcohol dehydrogenase is an example of a phase I reaction. Nicotinamide adenine dinucleotide phosphate (NADPH) is required for aromatic hydroxylation, an example of a phase I reaction.
8. **The answer is D.** First-pass metabolism simply means passage through the portal circulation before reaching the systemic circulation. In the face of liver dysfunction, drug levels may reach higher concentrations. Bioavailability of drugs is decreased, not increased, by the fraction removed after the first pass through the liver. Drugs are usually less rapidly metabolized when hepatic enzymes are elevated (which indicates hepatic dysfunction). Solubility of drugs is not associated with hepatic damage.

9. **The answer is A.** Dosing schedules of drugs are adjusted according to their half-lives to achieve steady-state plasma concentration. Attempting to avoid the toxicity of the drug because of its low therapeutic index (TI) represents an unlikely scenario; since to reduce toxicity of a drug with a low TI, one would reduce the dosing schedule, not increase it. Distribution of the drug is generally not affected by dosing schedule, nor is dose scheduling affected by first-pass metabolism. Some fluctuation in plasma concentration occurs even at steady state; it is the average concentration over time that is the goal of steady state.

10. **The answer is E.** To calculate the volume of distribution, use the formula in which the dose of the drug is divided by the plasma concentration. In this case, 0.25 mg is divided by 0.05 mg/L, giving the result of 5 L for volume of distribution.

11. **The answer is E.** For the plasma concentration of drug to decrease by 50%, half the drug present in the body initially must be eliminated. The amount of drug in the body initially is the volume of distribution × the plasma concentration (50 L × 4 mg/L = 200 mg). When the plasma concentration falls to 2 mg/L, the body will contain 100 mg of drug (50 L × 2 mg/L = 100 mg). Since the body eliminates the drug at a rate of 2 mg/h, it will require 50 hours for 100 mg of the drug to be eliminated.

12. **The answer is C.** A 100-mg tablet every 24 hours is a dose rate of 4.17 mg/h (100/24 = 4.17), which is the same dose rate as one 50-mg tablet every 12 hours (50/12 = 4.17). Thus, the average plasma concentration will remain the same, but *decreasing both* the dose and the dose interval will decrease the peak to trough variation of plasma concentration.

13. **The answer is B.** The *initial rate* of distribution of a drug to a tissue depends primarily on the rate of blood flow to that tissue. At longer times, however, a drug may undergo redistribution among various tissues, for example, a very lipophilic drug may become concentrated in adipose tissue with time.

14. **The answer is D.** The induction of the cytochrome P-450 following chronic administration will increase the conversion of the inactive prodrug to its active form. This will shift the dose–response curve of the prodrug to the left (i.e., increase its potency) without changing its efficacy.

15. **The answer is C.** The CYP3A subfamily is responsible for roughly 50% of the total cytochrome P-450 activity present in the liver and is estimated to be responsible for approximately half of all clinically important untoward drug interactions resulting from metabolism.

16. **The answer is D.** If the oral dosing rate is constant but the bioavailability increases, the fraction of the administered dose that reaches the general circulation unaltered increases. This, in turn, will increase the steady-state plasma concentration.

17. **The answer is B.** Steady-state plasma concentration of drug = (dose rate)/(clearance). Thus, a decrease in clearance will increase the plasma drug concentration, whereas an increase in any of the other three parameters will *decrease* the steady-state plasma concentration.

18. **The answer is C.** Inspection of the plasma concentration values indicates that the half-life of drug does not become constant until 1–9 hours after administration. The drug concentration decreases by half (from 50 to 25 mcg/L) between 1 and 5 hours (a 4-hour interval) and again decreases by half (from 25 to 12.5 mcg/L) between 5 and 9 hours (again, a 4-hour interval). This indicates the half-life of the drug is 4 hours. The rapid decrease in plasma concentration between 0 and 1 hour, followed by a slower decrease thereafter (and the constant half-life thereafter), indicates that this drug obeys a two-compartment model with an initial distribution phase followed by an elimination phase. The half-life is always determined from the elimination phase data.

19. **The answer is C.** Receptor affinity for the drug will determine the number of drug–receptor complexes formed. Efficacy is the ability of the drug to activate the receptor after binding has occurred. Therapeutic index (TI) is related to safety of the drug. Half-life and secretion are properties of elimination and do not influence the formation of drug–receptor complexes.

20. **The answer is D.** A noncompetitive antagonist decreases the magnitude of the response to an agonist but does not alter the agonist's potency (i.e., the ED_{50} remains unchanged). A competitive antagonist interacts at the agonist-binding site.

21. **The answer is D.** This drug will undergo filtration and passive reabsorption. Since the molecular weight of the drug is small, free drug will be filtered. Because 20% of the drug is bound to plasma proteins, 80% of it is free and available for filtration, which would be at a rate of 100 mL/min (i.e., 0.8 × 125 mL/min; 125 mL/min is the normal glomerular filtration rate [GFR]). A clearance of 10 mL/min must indicate that most of the filtered drug is reabsorbed.