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Katzung & Trevor's Pharmacology

Examination & Board Review

Anthony J. Trevor
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Susan B. Masters

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Katzung & Trevor's Pharmacology: Examination & Board Review, Sixth Edition

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Notice

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Preface

This book is designed to help students review pharmacology and to prepare for both regular course examinations and board examinations. The sixth edition has been extensively revised to make such preparation as efficient as possible. As with earlier editions, rigorous standards of accuracy and currency have been maintained, in keeping with the book's status as companion to the textbook *Basic & Clinical Pharmacology.* Several strategies are employed to make reviewing more effective.

First, the 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 review book in conjunction with course notes or a larger text.

Second, each chapter explicitly lists a set of objectives, providing students with a checklist against which they can challenge themselves as they progress through the book.

Third, each chapter provides a concise review of the core subject matter. Core content is based on careful analysis of the content of current board examinations as well as of major medical school courses. Tables of definitions and diagrams illustrating the major subdivisions within each drug group are provided.

Fourth, tables of important drug names are provided in each chapter dealing with specific drug groups. Recognition of drug names is important for both board and course examinations. Learning the names is made more efficient by distinguishing between drugs important as prototypes, those recognized as major variants, and those that should simply be recognized as belonging to a particular drug group.

Fifth, each chapter ends with practice questions followed by a list of answers and explanations. Questions that require analysis of graphic or tabular data are included. Most of the questions are of the "A" (single best answer) type in keeping with the format adopted by the United States Medical Licensure Examination (USMLE); many are set in the "clinical vignette" format currently favored. Case histories are included in 20 chapters, with questions and answers, providing additional review and testing of the student's preparation for questions about clinical pharmacology. A small proportion of questions are of the "R" (matching and extended matching) type. Appendices II and III present two complete examinations, each covering the entire field of pharmacology. More than 1150 questions (with answers) are provided in this book.

Sixth, Appendix I is an updated list of key drugs that appear frequently in board and course examination questions with concise key word descriptions of their characteristics. This learning aid serves also as an efficient flash-card list of the drugs and those drug properties most likely to appear on an examination.

When studying a discipline, it is important to continually review the basic principles and key information learned previously. To help students do this, most chapters now include a new Skill Keeper feature that consists of questions linking material in the chapter to information presented in previous chapters. Skill Keepers are intended to remind students of important principles discussed in earlier chapters and to facilitate the integration of drug information.

A short appendix on test strategies, which summarizes time-saving devices for approaching specific types of questions used on most objective examinations, is also included.

We recommend that this book be used with a regular text. *Basic & Clinical Pharmacology,* 8th edition (McGraw-Hill, 2001), 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 and Board Review* will greatly improve his or her performance on examinations 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 very grateful to these contributors, to our other faculty colleagues, and to our students—who have taught us most of what we know about teaching.

Suggestions and criticisms regarding this study guide should be sent to us at the following address: Department of Cellular and Molecular Pharmacology, Box 0450, University of California School of Medicine, San Francisco, CA 94143-0450, USA.

San Francisco
August 2001

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Contents

Part I: Basic Principles

Introduction 1

OBJECTIVES

You should be able to:

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

Learn the definitions that follow.

Table 1–1. Definitions.

Term	Definition
Pharmacology	The study of the interaction of chemicals with living systems
Drugs	Substances that act on living systems at the chemical (molecular) level
Drug receptors	The molecular components of the body with which a drug interacts to bring about its effects
Medical pharmacology	The study of drugs used for the diagnosis, prevention, and treatment of disease
Toxicology	The study of the undesirable effects of chemical agents on living systems; considered an area of pharmacology. In addition to the adverse effects of therapeutic agents on individuals, toxicology deals with the actions of industrial pollutants, natural organic and inorganic poisons, and other chemicals on species and ecosystems as well
Pharmacodynamics	The actions of a drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic action
Pharmacokinetics	The actions of the body on the drug, including absorption, distribution, metabolism, and excretion. 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

CONCEPTS

A. The Nature of Drugs:

1. **Size and molecular weight (MW):** Drugs in common use vary in size from MW 7 (lithium) to over MW 50,000 (thrombolytic enzymes). The majority of drugs, however, have molecular weights between 100 and 1000.
2. **Drug-receptor bonds:** Drugs bind to receptors with a variety of chemical bonds. These include very strong covalent bonds (which usually result in irreversible action), somewhat weaker electrostatic bonds (eg, between a cation and an anion), and much weaker interactions (eg, hydrogen, van der Waals, and hydrophobic bonds).

B. The Movement of Drugs in the Body: In order 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).

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

a. 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 below).

b. Lipid diffusion: Lipid diffusion is the movement of molecules through membranes and other lipid structures. Like aqueous diffusion, this is a passive process governed by Fick's law (see below).

c. Transport by special carriers: Drugs may be transported across barriers by mechanisms that carry similar endogenous substances, eg, the amino acid carriers in the blood-brain barrier and the weak acid carriers in the renal tubule. Unlike aqueous and lipid diffusion, carrier transport is not governed by Fick's law and is capacity-limited. Selective inhibitors for these carriers may have clinical value; eg, probenecid, which inhibits transport of uric acid, penicillin, and other weak acids, is used to increase the excretion of uric acid in gout. The family of P-glycoprotein transport molecules, previously identified as one cause of cancer drug resistance, has recently been identified in the epithelium of the gastrointestinal tract and appears to be responsible for expulsion of certain drugs into the intestinal lumen.

d. Endocytosis, pinocytosis: Endocytosis occurs through binding to specialized components (receptors) on cell membranes, with subsequent internalization by infolding of that area of the membrane. The contents of the resulting 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 peptides may enter cells by this mechanism. 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. Exocytosis is the reverse process, ie, the expulsion of membrane-encapsulated material from cells.

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

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

This relationship quantifies the observations that drug absorption is faster from organs with large surface areas, eg, the small intestine, than from organs with small absorbing areas, eg, 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.

3. Water and lipid solubility of drugs:

a. Aqueous diffusion: 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 proportionate to its charge.

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

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

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

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

The following equations summarize these points:

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

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

The Henderson-Hasselbalch relationship is clinically important when it is necessary to accelerate the excretion of drugs by the kidney, eg, in the case of an overdose. Most drugs are freely filtered at the glomerulus, but lipid-soluble drugs can be rapidly reabsorbed from the tubular urine. When a patient takes an overdose of a weak acid drug, its excretion may be accelerated by alkalinizing the urine, eg, by giving bicarbonate. 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. Conversely, excretion of a weak base may be accelerated by acidifying the urine, eg, by administering ammonium chloride (Figure 1–1).

C. Absorption of Drugs:

1. **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 bloodstream). The rate and efficiency of absorption differ depending on a drug's route of administration. In fact, for some drugs, the amount absorbed into the circulation may be only a small fraction of the dose administered

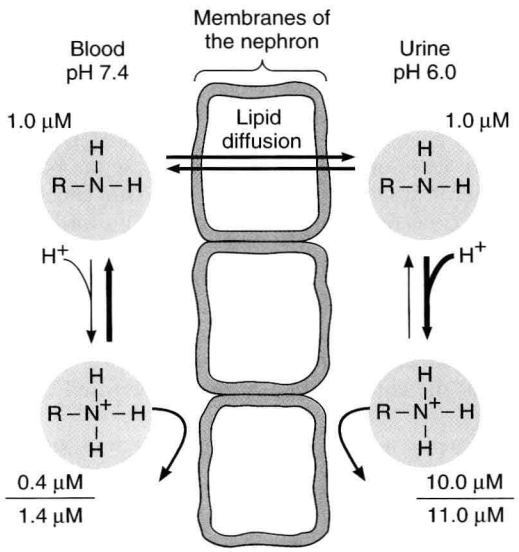

Figure 1–1. "Trapping" is a method for accelerating excretion of drugs. Because the nonionized form diffuses readily across the lipid barriers of the nephron, this form will equilibrate and may reach equal concentrations in the blood and urine; the ionized form will not. Protonation will occur within 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 eight times higher than the blood concentration.

when given by certain routes. The amount absorbed divided by the amount administered constitutes its **bioavailability.** Common routes of administration and some of their features include the following:

a. **Oral (swallowed):** The oral route offers maximum convenience, but absorption may be slower and less complete than when parenteral routes are used. Ingested drugs are subject to the **first-pass effect,** in which a significant amount of the agent is metabolized in the gut wall and the liver before it reaches the systemic circulation. Thus, some drugs have low bioavailability when given orally.

b. **Intravenous:** The intravenous route offers instantaneous and complete absorption (by definition, bioavailability is 100%). This route is potentially more dangerous, however, because of the high blood levels that are produced if administration is too rapid.

c. **Intramuscular:** Absorption from an intramuscular injection site is often (not always) faster and more complete (higher bioavailability) than with oral administration. Large volumes (eg, > 5 mL into each buttock) may be given. First-pass metabolism is avoided.

d. **Subcutaneous:** The subcutaneous route offers slower absorption than the intramuscular route. Large volume bolus doses are less feasible. First-pass metabolism is avoided.

e. **Buccal and sublingual:** The buccal route (in the pouch between gums and cheek) permits direct absorption into the systemic venous circulation, bypassing the hepatic portal circuit and first-pass metabolism. This process may be fast or slow depending on the physical formulation of the product. The sublingual route (under the tongue) offers the same features as the buccal route.

f. **Rectal (suppository):** The rectal route offers partial avoidance from the first-pass effect (though not as completely as the sublingual route). Larger amounts of drug and drugs with unpleasant taste are better administered rectally than by the buccal or sublingual routes. Some drugs administered rectally may cause significant irritation.

g. **Inhalation:** In the case of respiratory diseases, the inhalation route offers delivery closest to the target tissue. This route often provides rapid absorption because of the large alveolar surface area available.

h. **Topical:** The topical route includes application to the skin or to the mucous membrane of the eye, nose, throat, airway, or vagina for *local* effect. The rate of absorption varies with the area of application and the drug formulation, but is usually slower than any of the routes listed above.

i. **Transdermal:** The transdermal route involves application to the skin for *systemic* effect. Absorption usually occurs very slowly, but the first-pass effect is avoided.

D. Distribution of Drugs:

1. **Determinants of distribution:** The distribution of drugs to the tissues depends upon the following:

   a. **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.

   b. **Blood flow:** Blood flow to the tissue is an important determinant of the *rate* of uptake, although blood flow may not affect the steady state amount of drug in the tissue. As a result, well-perfused tissues (eg, brain, heart, kidneys, splanchnic organs) will often achieve high tissue concentrations sooner than poorly perfused tissues (eg, fat, bone). If the drug is rapidly eliminated, the concentration in poorly perfused tissues may never rise significantly.

   c. **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 (including the brain) have a high lipid content and thus dissolve a high

concentration of lipid-soluble agents. As a result, a very lipid-soluble anesthetic will transfer out of the blood and into the brain tissue to a greater extent than a drug with low lipid solubility.

d. **Binding:** Binding of a drug to macromolecules in the blood or a tissue compartment will tend 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 to tissue proteins, which results in a marked reduction in the plasma concentration of chloroquine.

2. **Apparent volume of distribution:** The apparent volume of distribution (V_d) is an important pharmacokinetic parameter that reflects the above determinants of drug distribution in the body. V_d relates the amount of drug in the body to the concentration in the plasma. (See Chapter 3 and Table 1–2.)

E. Metabolism of Drugs: 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 above as one cause of low bioavailability. Other drugs are administered as inactive **prodrugs** and must be metabolized to active agents. Some drugs are not metabolized at all—their action must be terminated by excretion.

1. **Drug metabolism as a mechanism of termination of drug action:** The action of many drugs (eg, phenothiazines) is terminated before they are excreted because they are metabolized to biologically inactive derivatives.
2. **Drug metabolism as a mechanism of drug activation: Prodrugs** (eg, levodopa, methyldopa, parathion) 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, many benzodiazepines.
3. **Drug elimination without metabolism:** Some drugs (eg, lithium) are not modified by the body; they continue to act until they are excreted.

F. Elimination of Drugs: Along with the dosage, the rate of elimination (disappearance of the active molecule from the bloodstream or body) determines the duration of action for most drugs. Therefore, knowledge of the time course of concentration in plasma is important 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. Furthermore, 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 alpha adrenoceptors, is eliminated from the bloodstream in an hour or less after administration. The drug's action, however, lasts for 48 hours.

1. **First-order elimination:** The term *first-order elimination* implies that the rate of elimination is proportionate 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 1–2, left). Drugs with first-order elimination have a characteristic **half-life of elimination** that is constant regardless of the amount

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

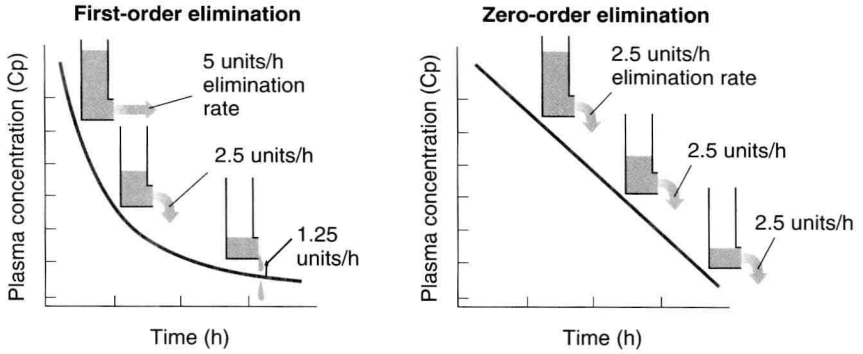

Figure 1–2. Comparison of first-order and zero-order elimination. For drugs with first-order kinetics (left panel), rate of elimination is proportionate to concentration; in the case of zero-order elimination (right panel), the rate is constant and independent of concentration.

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.

2. **Zero-order elimination:** The term *zero-order elimination* implies that the rate of elimination is constant regardless of concentration (Figure 1–2, right panel). A few drugs saturate their elimination mechanisms even at low concentrations. As a result, the drug's concentration in plasma decreases in a linear fashion over time. This is typical of ethanol (over most of its plasma concentration range) and of phenytoin and aspirin at high therapeutic or toxic concentrations.

G. Pharmacokinetic Models:

1. **Multicompartment distribution:** After absorption, many drugs undergo an early distribution phase followed by a slower elimination phase. Mathematically, this behavior can be modeled by means of a "two-compartment model" as shown in Figure 1–3. (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.)
2. **Single-compartment distribution:** A few drugs may behave as if they are distributed to only one compartment (eg, if they are restricted to the vascular compartment). Others have more complex distributions that require more than two compartments for construction of accurate mathematical models.

QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 3-year-old child is brought to the emergency department having just ingested a large overdose of promethazine, an antihistaminic drug. Promethazine is a weak base with a pK_a of 9.1. It is capable of entering most tissues, including the brain. On physical examination, the heart rate is 100/min, blood pressure 110/60 mm Hg, and respiratory rate 20/min. In this case of promethazine overdose,
   (A) Urinary excretion would be accelerated by administration of NH_4Cl
   (B) Urinary excretion would be accelerated by giving $NaHCO_3$
   (C) More of the drug would be ionized at blood pH than at stomach pH
   (D) Absorption of the drug would be faster from the stomach than from the small intestine
   (E) Hemodialysis is the only effective therapy
2. All of the following are general mechanisms of drug permeation EXCEPT
   (A) Aqueous diffusion
   (B) Aqueous hydrolysis
   (C) Lipid diffusion
   (D) Pinocytosis or endocytosis
   (E) Special carrier transport

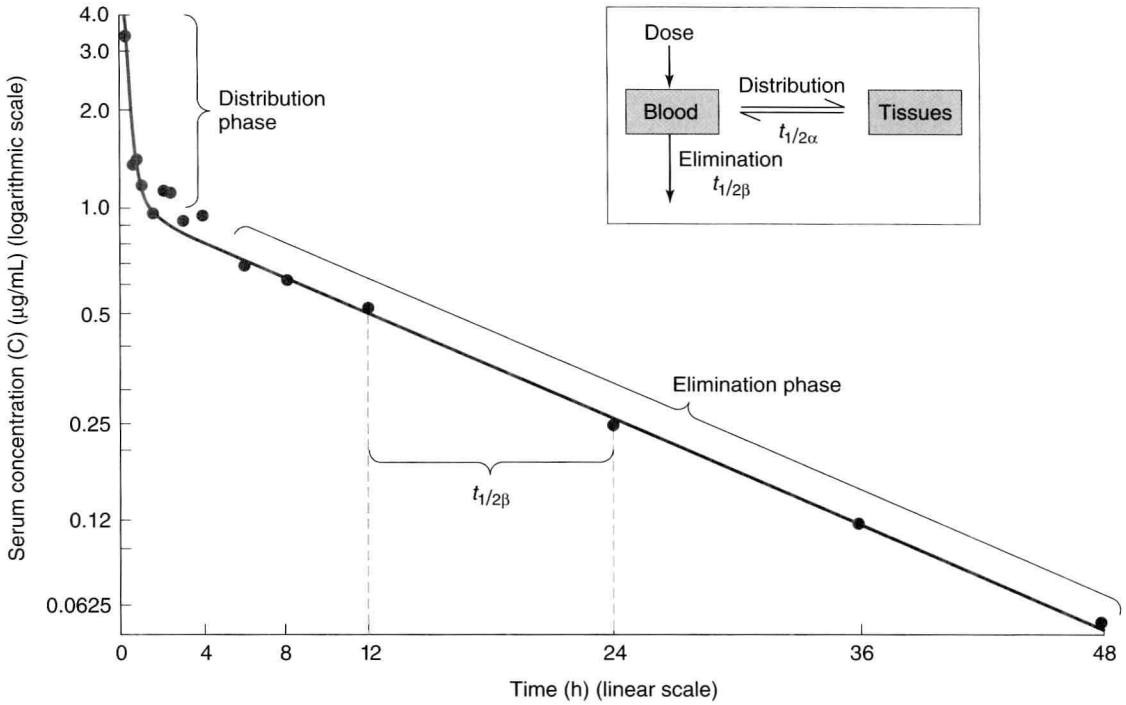

Figure 1–3. Serum concentration-time curve after administration of chlordiazepoxide as an intravenous bolus. The experimental data are plotted on a semilogarithmic scale as filled circles. This drug follows first-order kinetics and appears to occupy two compartments. The initial curvilinear portion of 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 two plasma concentration points that differ by twofold. (See Chapter 3 for additional details.) (Modified and reproduced, with permission, from Greenblatt DJ, Koch-Weser J: Drug therapy: Clinical pharmacokinetics. N Engl J Med 1975;293:702.)

3. A patient with a history of episodic attacks of coughing, wheezing, and shortness of breath is being evaluated in the asthma clinic. Several drug treatments with different routes of administration are under consideration. Which of the following statements about routes of administration is MOST correct?
   (A) Blood levels often rise more slowly after intramuscular injection than after oral dosing
   (B) The "first-pass" effect is the result of metabolism of a drug after administration and before it enters the systemic circulation
   (C) Administration of antiasthmatic drugs by inhaled aerosol is usually associated with more adverse effects than is administration of these drugs by mouth
   (D) Bioavailability of most drugs is greater with rectal (suppository) administration than with sublingual administration
   (E) Administration of a drug by transdermal patch is often faster but is associated with more first-pass metabolism than oral administration
4. Aspirin is a weak organic acid with a pK_a of 3.5. What percentage of a given dose will be in the lipid-soluble form at a stomach pH of 2.5?
   (A) About 1%
   (B) About 10%
   (C) About 50%
   (D) About 90%
   (E) About 99%
5. If the plasma concentration of a drug declines with "first-order kinetics," this means that
   (A) There is only one metabolic path for drug disposition
   (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 proportionate to the rate of administration at all times
(E) The drug is not distributed outside the vascular system

6. Regarding termination of drug action,
(A) Drugs must be excreted from the body to terminate their action
(B) Metabolism of drugs always increases their water solubility
(C) Metabolism of drugs always abolishes their pharmacologic activity
(D) Hepatic metabolism and renal excretion are the two most important mechanisms involved
(E) Distribution of a drug out of the bloodstream terminates the drug's effects

7. Distribution of drugs to specific tissues
(A) Is independent of blood flow to the organ
(B) Is independent of the solubility of the drug in that tissue
(C) Depends on the unbound drug concentration gradient between blood and the tissue
(D) Is increased for drugs that are strongly bound to plasma proteins
(E) Has no effect on the half-life of the drug

8. Pilocarpine is being considered for the treatment of glaucoma in a 58-year-old patient. Except for elevated intraocular pressure, the patient's history and physical exam are unremarkable. Pilocarpine is a weak base of pK_a 6.9. Which of the following statements is FALSE?
(A) After parenteral administration, the concentration of pilocarpine in the aqueous humor (pH 7.8) will be lower than the concentration in the duodenum (pH 5.5)
(B) When administered as eye drops, absorption into the eye will be faster if the drops are alkaline (pH 8.0) than if they are acidic (pH 5.0)
(C) Excretion in the urine will be faster if urine pH is alkaline (pH 8.0) than if the urine pH is acidic (pH 5.8)
(D) The proportion of pilocarpine in the protonated form will be approximately 90% at pH 5.9
(E) The proportion of pilocarpine in the more lipid soluble form will be approximately 99% at pH 8.9

9. For which of the following drugs will excretion be most significantly accelerated by acidification of the urine?
(A) Weak acid with pK_a of 5.5
(B) Weak base with pK_a of 3.5
(C) Weak acid with pK_a of 7.5
(D) Weak base with pK_a of 6.5

10. A physical process by which a weak acid becomes less water-soluble and more lipid-soluble at low pH is:
(A) Distribution
(B) Elimination
(C) First-pass effect
(D) Permeation
(E) Protonation

DIRECTIONS (Items 11–15): Each set of matching questions in this section consists of a list of lettered options followed by several numbered items. For each numbered item, select the ONE lettered option that is most closely associated with it. Each lettered option may be selected once, more than once, or not at all.

Items 11–15:

(A) Distribution
(B) Elimination
(C) Endocytosis
(D) First-pass effect
(E) First-order kinetics
(F) Lipid solubility
(G) Permeation
(H) Pharmacodynamics
(I) Pharmacokinetics

(J) Protonation
(K) Volume of distribution
(L) Zero-order kinetics

11. Properties that characterize the effects of a drug on the body
12. Properties that describe the effects of the body on a drug
13. Process by which the amount of active drug in the body is reduced after absorption into the systemic circulation
14. Process by which drug in the body is reduced after administration but before entering the systemic circulation
15. Kinetics that are characteristic of the excretion of ethanol and high doses of phenytoin and aspirin

ANSWERS

1. Questions that deal with acid-base (Henderson-Hasselbalch) manipulations are common. Since absorption involves permeation across lipid membranes, we can 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. Promethazine is a weak base—which means that it will be more ionized (protonated) at acid pH than at basic pH. Choice **(C)** suggests that the drug would be more ionized at pH 7.4 than at pH 2.0: clearly wrong. **(D)** says (in effect) that the more ionized form will be absorbed faster, and that is wrong. **(A)** and **(B)** are opposites, since NH_4Cl is an acidifying salt and sodium bicarbonate an alkalinizing one. From the point of view of test strategy, opposites always deserve careful attention and, in this case, encourage us to exclude **(E),** a distracter. Since an acid environment favors ionization of a weak base, we should give NH_4Cl. The answer is **(A).**
2. Hydrolysis has nothing to do with the mechanisms of permeation; rather, hydrolysis is one mechanism of drug metabolism. The answer is **(B).**
3. Blood levels usually rise more *rapidly* after intramuscular injection than after oral administration. **(C)** is wrong: delivering the drug directly to the target organ usually *reduces* adverse effects, because the required total dose is smaller and the concentration reaching other organs is lower. Bioavailability is usually greater after sublingual than after rectal administration. This is because suppositories tend to migrate upward in the rectum and absorption from this location is partially into the portal circulation. Onset of effect is usually slower with transdermal administration than with any other route; but it does permit absorption directly into the systemic venous circulation. The answer is **(B).**
4. Aspirin is an acid, so it will be more ionized at alkaline pH and less ionized at acidic pH. The Henderson-Hasselbalch equation predicts that the ratio will change from 50/50 at the pH equal to the pK_a to 10/1 (protonated/unprotonated) at 1 pH unit more acidic than the pK_a. For acids, the protonated form is the nonionized, more lipid-soluble form. The answer is **(D).**
5. See pages 5–6 of this unit. First-order means that the elimination rate is proportionate to the concentration perfusing the organ of elimination. One result of this proportionality is that a plot of the logarithm of the plasma concentration on the vertical axis versus time on the horizontal axis is a straight line. The half-life is a constant. The rate of elimination is proportionate to the rate of administration only at steady state. Zero-order elimination means that a constant number of moles or grams are eliminated per unit time regardless of the plasma concentration. The half-life will then be concentration-dependent and is not a useful variable. Ethanol is the most common drug with zero-order elimination. The answer is **(B).**
6. Note the "trigger" words ("must," "always") in choices **(A), (B),** and **(C).** All drugs that affect tissues other than the blood or vascular endothelium act outside of the "bloodstream." The answer is **(D).**
7. This is a straightforward question of distribution concepts. There are no trigger words to give the answer away, but it can be deduced without much trouble. From the list of determinants of drug distribution given previously, choice **(C)** is correct.
8. More Henderson-Hasselbalch concepts. Weak bases are more protonated in an acidic environment because more protons (hydrogen ions) are available. In the protonated state, weak bases are ionized, polar, and less lipid soluble. Therefore, less pilocarpine is lipid-soluble and able to diffuse through the duodenum (pH 5.5) than is able to diffuse through the surface of the eye (pH 7.8). By the same reasoning, the drug diffuses faster if the eye drops are alkaline than if