Pharmacology

Examination and Board Review

Second Edition

a LANGE medical book

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Bertram G. Katzung, MD, PhD
Professor of Pharmacology
Department of Pharmacology
University of California, San Francisco

Anthony J. Trevor, PhD
Professor of Pharmacology and Toxicology
Department of Pharmacology
University of California, San Francisco

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Preface

Preparing for a large "board type" examination is a difficult task. It is with good reason, then, that students seek a review or study guide that can make the process more efficient. This book takes a unique approach to the challenge, an approach that has been well tested by successful students over a 5-year period.

First, the book breaks the subject down into the topics used in most courses and textbooks, rather than combining them into larger, unwieldy groups. Major introductory sections (e.g., autonomic pharmacology and CNS pharmacology) are included, so that students can integrate their review of pharmacology with a review of physiology and biochemistry. This chapter-based approach also encourages students to use the *Review*, in conjunction with their course notes or with a larger text.

Second, it explicitly lists the objectives in each unit, providing students with a checklist against which they can challenge themselves as they progress through the book.

Third, each chapter provides a concise and highly organized review of the material that is considered core subject matter by experts in the field. The determination of what is core is based on a careful analysis of the content of actual board examinations over the past several years as well as the content of major medical school courses.

Fourth, a table of important drug names is provided in every chapter dealing with a specific drug group. Recognition of drug names is an important part of board exams. We make the process more efficient by distinguishing between those drugs important as prototypes, those recognized as major variants on the prototypes, and those that should simply be recognized as belonging to a particular drug group.

Finally, each chapter ends with a generous sampling of questions followed by a list of answers and explanations. Because each area of pharmacology is represented by a separate chapter, students are assured of having practice questions in every important area. Questions that require analysis of graphic data or short case descriptions are included. Approximately 95% of the questions can be answered from material presented in the book.

The book provides several additional sections of value to the student preparing for a board exam: (1) two full examinations, which together cover the entire field in an integrated manner, giving the student practice questions that combine drugs from several different groups; (2) a set of 18 case histories, with questions and answers, providing additional review and testing of the student's preparation for questions about clinical pharmacology; and (3) a short chapter on test strategies, which summarizes time-saving devices for approaching specific types of questions used on most board exams.

It is recommended that this book be used with a regular text. The reader will find that *Basic & Clinical Pharmacology*, by Katzung (Appleton & Lange, 1989), follows the same sequence used here. However, the *Review* is designed to complement any standard medical pharmacology text.

Because it was developed in parallel with the textbook *Basic & Clinical Pharmacology*, the *Review* represents the authors' interpretations of chapters written by contributors to that text. We are very grateful to these authors, 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 mailed to us at the following address:
Pharmacology Department, Box 0450
University of California
San Francisco, CA 94143-0450, USA

Bertram G. Katzung, MD, PhD
Anthony J. Trevor, PhD
San Francisco
September 1989

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Part I. Basic Principles

Introduction 1

OBJECTIVES

Define the following terms:

- Absorption
- Distribution
- Drug
- Elimination
- Excretion
- Metabolism
- Permeation
- Pharmacodynamics
- Pharmacokinetics
- Pharmacology
- pK_a
- Special carrier
- Termination of action
- Toxicology
- Weak acid, weak base
- Zero-order, first-order elimination

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.

GENERAL DEFINITIONS

A. Pharmacology: The study of the interaction of chemicals with living systems.

B. Drugs: Chemicals that act on living systems at the chemical (molecular) level.

C. Medical Pharmacology: The study of drugs used for the diagnosis, prevention, and treatment of disease.

D. Toxicology: The study of the untoward effects of chemical agents on living systems. It is usually considered an area of pharmacology.

E. Pharmacodynamic Properties: The action of a drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic action.

F. Pharmacokinetic Properties: The action of the body on the drug, including absorption, distribution, metabolism, and excretion. Elimination of a drug may be achieved by metabolism or by excretion.

CONCEPTS

A. Permeation: The movement of drug molecules within the biologic environment. Permeation involves several processes. The 4 most important are the following:

(1) Aqueous diffusion: Simple diffusion through the watery extracellular and intracellular spaces.

(2) Lipid diffusion: Solution in and diffusion through membranes and other lipid structures.

(3) Transport by special carriers: Transport across barriers by carrier mechanisms developed for related endogenous substances, eg, the secretory and reabsorptive carriers for weak acids located in the renal tubule.

(4) Pinocytosis: Binding to specialized components of the membrane with subsequent internalization by infolding of that area of the membrane. Some drugs, especially peptides, enter cells by this mechanism.

B. Water & Lipid Solubility of Drugs:

(1) The aqueous solubility of a drug is often a function of the electrostatic charge on the molecule, because water molecules behave as dipoles. Conversely, the lipid solubility is inversely proportionate to the charge.

(2) A large number of drugs are weak bases or weak acids. The pH of the medium determines the fraction of molecules charged (ionized) if the molecule is a weak acid or base. If the pK_a of the drug and the pH of the medium are known, this fraction can be predicted by means of the Henderson-Hasselbalch equation:

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

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

(3) Weak bases are ionized—and therefore more polar and more water-soluble—when they are protonated; weak acids are less ionized—and so less water-soluble—when they are protonated.

C. Absorption of Drugs:

(1) Drugs usually enter the body at sites remote from the target tissue or organ and must be carried by the circulation to the intended site of action. Before a drug can enter the bloodstream, it must be absorbed; the rate and efficiency of absorption differs depending on the **route of administration.** Common routes of administration of drugs and some of their features include the following:

(a) Oral (swallowed): Offers maximum convenience but may be slower and less complete than parenteral routes. Subject to the **first-pass effect** (metabolism of a significant amount of the agent in the gut wall and the liver before it reaches the systemic circulation).

(b) Buccal (in the pouch between gums and cheek): Permits direct absorption into the systemic venous circulation, bypassing the hepatic portal circuit and first pass metabolism. May be fast or slow depending on the physical formulation of the product.

(c) Sublingual (under the tongue): Offers the same features as the buccal route.

(d) Rectal (suppository): Offers the same advantage as the buccal route, but larger amounts are feasible. Some drugs may cause irritation.

(e) Intramuscular: Absorption sometimes (not always) faster and more complete than it is with oral administration. Large volumes (eg, 5–10 mL) may be given.

(f) Subcutaneous: Offers slower absorption than intramuscular. Large volumes are not feasible.

(g) Inhalation: In the case of respiratory diseases, offers delivery closest to the target organ; often provides rapid absorption because of the large alveolar surface area available.

(h) Topical: Application to the skin or 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 it is usually slower than any of the routes listed above.
(i) Transdermal: Application to the skin for *systemic* effect. Absorption usually occurs very slowly, but first-pass effect is avoided.
(j) Intravenous: Offers instantaneous and complete absorption (by definition, 100%); potentially more dangerous.

D. Distribution of Drugs:

(1) The distribution of drugs to the various tissues depends upon the following:
(a) Size of the organ. For example, skeletal muscle is a very large organ and can take up a large amount of drug. In contrast, the brain is smaller and therefore will achieve the same drug concentration with a much smaller amount of drug if other factors are equal.
(b) Blood flow to the tissue (important in the *rate* of uptake).
(c) Solubility of the drug in the tissue. For example, some organs (eg, the brain) have a high lipid content and thus dissolve a higher concentration of lipid-soluble agents.
(d) Binding of the drug to macromolecules in the blood or tissue.

(2) The **apparent volume of distribution** (Vd) is an important pharmacokinetic parameter that relates the amount of drug in the body to the concentration in the plasma. See Chapter 3.

E. Metabolism of Drugs:

(1) The action of many drugs (eg, local anesthetics, phenothiazines) is terminated before they are excreted because they are metabolized (chemically converted) to biologically inactive derivatives.

(2) Some drugs (**pro-drugs,** eg, levodopa) are inactive as administered and must be metabolized in the body to become active.

(3) Other drugs (eg, lithium) are not modified by the body and continue to act until they are excreted.

F. Elimination of Drugs:

(1) The **rate of elimination** (disappearance of the active molecule from the bloodstream or body) is usually related to termination of effect. A knowledge of the time course of a drug's concentration in plasma is therefore important in describing the intensity and duration of its effect. ***Note:*** *Elimination* is not the same as *excretion:* a drug may be eliminated by metabolism long before the molecules are excreted from the body. Conversely, for drugs with active metabolites (eg, diazepam), elimination by metabolism is *not* synonymous with termination of action. For drugs (like penicillin G) that are not metabolized, excretion is the mode of elimination.
(a) First-order elimination: First order implies that the rate of elimination is proportionate to the concentration; the result is that the drug's concentration in plasma decreases exponentially with time. Drugs with first-order elimination have a characteristic **half-life of elimination** that is constant regardless of the amount in the body. The concentration of such a drug in the blood will decrease by 50% for every half-life. Most of the drugs in clinical use demonstrate first-order kinetics.
(b) Zero-order elimination: Zero order implies elimination at a constant rate regardless of concentration. 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) Many drugs undergo an early distribution phase, followed by a slower elimination phase, after intravenous administration. Mathematically, this behavior can be modeled by means of a

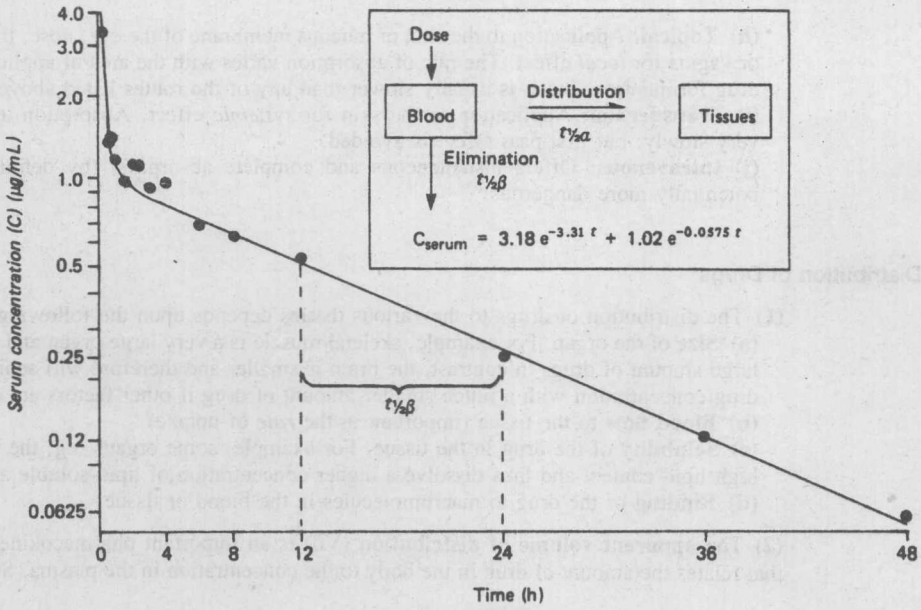

Figure 1–1. Serum concentration-time curve after administration of 25 mg of chlordiazepoxide as an intravenous bolus to a 75-kg man. The experimental data are plotted on a semilogarithmic scale as filled circles. If the drug is assumed to follow 2-compartment kinetics (inset), the initial curvilinear portion of the data represents the distribution phase, with drug moving into the tissues. The linear portion of the curve represents drug elimination. The equation shown in the inset was fitted to the data and generated the smooth curve passing through the data points. The elimination half-life ($t_{1/2\beta}$) can be extracted in two ways: graphically, by measuring the time between any 2 points that differ by 2-fold plasma concentration; and numerically, from the exponent of the second term of the equation, ie, $t_{1/2\beta}$ = 0.693 ÷ 0.0575 = 12 hours. (t = time). 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.)

"2 compartment model" as shown in Fig 1–1. (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, etc.)

(2) A few drugs may behave as though 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 2 compartments for accurate modeling.

Questions

DIRECTIONS (items 1–4): Each numbered item or incomplete statement 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. All of the following are mechanisms of drug permeation EXCEPT
(A) Aqueous diffusion.
(B) Aqueous hydrolysis.
(C) Lipid diffusion.
(D) Pinocytosis or endocytosis.
(E) Special carrier transport.

2. Promethazine is an antihistaminic drug. It is a weak base with a pK_a of 9.1. In the treatment of an overdose of the drug,
(A) Urinary excretion would be accelerated by administration of NH_4Cl.

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(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 for overdose.

3. Comparison of routes of drug administration shows that
(A) Blood levels always rise faster after intramuscular injection than after oral dosing.
(B) Intramuscular and subcutaneous routes are usually associated with greater discomfort at the site of administration than are the other routes.
(C) Administration of antiasthmatic drugs by aerosol is usually associated with more side effects than is giving the drug systemically.
(D) Bioavailability of most drugs is less with oral administration than with other routes.
(E) Both (B) and (D) are correct.

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) 1%.
(B) 10%.
(C) 50%.
(D) 90%.
(E) 99%.

DIRECTIONS (item 5): This item consists of lettered headings followed by a numbered phrase. Select the ONE lettered heading that is most closely associated with the phrase.

(A) Weak acid with pK_a of 2.5.
(B) Weak base with pK_a of 2.5.
(C) Weak acid with pK_a of 7.5.
(D) Weak base with pK_a of 7.5.

5. Excretion may be significantly accelerated by acidification of the urine.

DIRECTIONS (items 6–10): For each item in this section, ONE or MORE of the numbered options are correct. Select

A if only **(1), (2), and (3)** are correct;
B if only **(1) and (3)** are correct;
C if only **(2) and (4)** are correct;
D if only **(4)** is correct;
E if all are correct.

6. If the plasma concentration of a drug declines with "first-order kinetics," it means that
(1) There is only one metabolic path for drug disposition.
(2) The half-life is the same regardless of plasma concentration.
(3) The drug is largely metabolized in the liver after oral administration and has low bioavailability.
(4) The rate of elimination is proportionate to the plasma concentration.

7. Which of the following statements is (are) correct?
(1) Pharmacodynamic parameters characterize the effects of a drug on the body.
(2) Pharmacokinetic parameters describe the effects of the body on a drug.
(3) A "receptor" is that component of the body with which a drug interacts to produce its effects.
(4) Most useful drugs are between MW (molecular weight) 1500 and MW 15,000.

8. Regarding the termination of action of drugs that have no endogenous counterparts,
(1) Drugs must be excreted from the body to terminate their action.
(2) Metabolism of drugs always increases their water solubility.
(3) Metabolism of drugs always abolishes their pharmacologic activity.
(4) Hepatic metabolism and renal excretion are the 2 most important mechanisms.

9. Distribution of drugs to tissues
(1) Depends on blood flow and size of the organ.
(2) Depends on the solubility of the drug in that tissue.

(3) Depends on the concentration gradient between blood and tissue.
(4) Is increased for drugs that are strongly bound to plasma proteins.

10. Physiologic blood flows and volumes are important in drug distribution because
(1) Resting skeletal muscle receives the largest fraction of the cardiac output.
(2) Drugs that are restricted to the plasma vascular space have a volume of distribution of about 4% of body weight.
(3) In pregnancy, the placenta and uterus receive the largest fraction of the cardiac output.
(4) Drugs that are strongly bound to proteins outside the vascular space may have a volume of distribution greater than the body volume.

Answers

1. Hydrolysis is the only process listed that is *not* a regular mechanism of permeation. The answer is **(B).**

2. Here is one form of a favorite—the acid-base Henderson-Hasselbalch question. Since absorption involves permeation across lipid membranes, we can decrease absorption from the gut and from the tubular urine by making the drug less lipid-soluble. We know that ionization attracts water molecules and decreases lipid solubility. The drug is a weak base—which means that it will be more ionized (protonated) at acid pHs than at basic ones. All of the choices are variations on the theme of lipid permeation. Choice **(C)** puts it directly: it suggests that the drug would be more ionized at pH 7.4 than at pH 2. So **(C)** is 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 alkalizing one. From a purely test strategy point of view, opposites always deserve careful attention and, in this case, permit us to exclude **(E),** a distractor. If we consider the fact that lipid solubility favors reabsorption from the renal tubule back into the body, it should be clear that ionizing the molecule would reduce reabsorption. Since an acid environment favors ionization, we should give NH_4Cl. The answer is **(A).**

3. Choice **(A)** is right most of the time, but it uses the trigger word "always"; that makes it almost certainly wrong (read Appendix II). A few drugs, eg, diazepam, are absorbed poorly from intramuscular injection sites. Some formulations involve dissolving the drug in oil to deliberately achieve prolonged effects. **(B)** is true: These routes may cause discomfort. **(C)** is clearly the reverse of a reasonable choice, and **(D)** is correct: Although absorption may be good, the drug will be carried immediately to the liver, where metabolism may take place. The only single correct answer, therefore, is **(E).**

4. Henderson-Hasselbalch principles again. The drug is an acid, so it will be more ionized at basic pHs. The equation says 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 acid than the pK_a. For acids, the protonated form is the nonionized, more lipid-soluble form. The answer is **(D).**

5. Since acceleration of excretion requires an increase in the ionized fraction in the urine, the basic drugs are the ones to be considered here. How much would their excretion be affected by the degree of urinary acidification that is achievable (ie, from pH 8 to 5.5)? Clearly, a basic drug with a pK_a much lower than this range will not be significantly ionized: The drug of pK_a 2.5 will go from 1 part in 300,000 ionized at pH 8 to 1 part in 1000 ionized at pH 5.5—ie, less than 0.1% change in the nonionized fraction. In contrast, the basic drug of pK_a 7.5 is about 32% ionized, 68% nonionized at pH 8 but changes to 1% nonionized, 99% ionized at pH 5.5. The answer is **(D).**

6. Definitions, see above. First-order means that the elimination is proportionate to the concentration perfusing the organ of elimination. The result 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. (Zero-order elimination means that a constant number of moles or grams are eliminated per unit of time, regardless of 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 **(C).**

7. More definitions. **(1), (2),** and **(3)** are correct, so the answer is **(A).**

8. Note the "trigger" words (must, always) in choices **(1), (2),** and **(3).** The answer is **(D).**

9. Fairly straightforward. There are no trigger words to give the answer away, but it can be reasoned out without much trouble. Only choice **(4)** is unreasonable; the answer is **(A).**

10. Choice **(1)** is wrong because *resting* muscle is specified. At rest, skeletal muscle receives about 16% of the cardiac output while the liver receives 28% and the kidneys 23%. During maximal exercise, muscle would indeed receive the largest fraction of cardiac output. The answer is **(C).**

Pharmacodynamics 2

OBJECTIVES

Define the following terms:

- Chemical antagonist
- Competitive antagonist
- Coupling protein
- Drug efficacy
- Drug potency
- ED50, TD50, LD50
- Effector mechanism
- Graded dose-response curve
- Irreversible antagonist
- Partial agonist
- Physiologic antagonist
- Quantal dose-response curve
- Receptor
- Receptor agonist
- Spare receptor

You should be able to:

- Specify whether an antagonist is competitive or irreversible based on its effect on the dose-response curve of the agonist.
- Compare the efficacy and potency of drugs on the basis of their dose-response curves.
- Predict the effect of a partial agonist on a system in the presence and in the absence of a full agonist.
- Name an important inert binding-site protein in blood.
- Predict the effect of adding drug *B* when a barely subtoxic dose of drug *A* is present if drug *A* and drug *B* both bind to the same inert binding sites.
- Give examples of partial agonists, competitive and irreversible antagonists, and physiologic and chemical antagonists.
- Name the coupling and effector proteins that are activated by the beta-adrenoceptor.
- Name 4 methods by which drug-receptor signals bring about effects.

DEFINITIONS & CONCEPTS

A. Receptors: Receptors are those specific molecular components of a biologic system with which drugs interact to produce changes in the function of the system. Receptors must be selective in their ligand-binding characteristics (so as to respond to the proper chemical signal and not to meaningless ones) and they must be modifiable as a result of binding (to bring about the functional change). Receptors have been identified, isolated, purified, and chemically characterized. The receptors characterized to date are proteins and other macromolecules such as

DNA. The **receptor site** for a drug appears to be a specific area of the macromolecule that has a high and specific affinity for the drug molecule. The interaction of a drug with its receptor is the fundamental event that initiates the action of the drug.

B. Spare Receptors: Spare receptors are said to exist when the maximum drug response is obtained at less than saturation (complete occupation) of the receptors. The effect of having spare receptors in a system is to increase its sensitivity to the agonist.

C. Inert Binding Sites: Inert binding sites are sites on endogenous molecules that bind a drug without initiating events leading to the drug's effects. In many compartments of the body (eg, the plasma), they play an important role in buffering the concentration of a drug. The 2 most important plasma proteins with significant binding capacity are albumin and orosomucoid.

D. Agonist, Partial Agonist: An agonist is a drug capable of fully activating the effector system when it binds to the receptor. A partial agonist produces less than the full effect, even when it has saturated the receptors (Fig 2–1). In the presence of a full agonist, a partial agonist acts like a competitive inhibitor.

E. Competitive & Irreversible Antagonists: Competitive antagonists are drugs that bind to the receptor in a reversible way without activating the effector system for that receptor. Their effect can be overcome by adding more agonist. Irreversible antagonists cannot be overcome by adding more agonist. The graded dose-response curves generated in the presence of these 2 types of inhibitors differ (Fig 2–2).

F. Physiologic Antagonist: This denotes a drug that binds to some other receptor, producing an effect opposite to that produced by the drug it is antagonizing.

G. Chemical Antagonist: This denotes a chelator or similar agent that interacts directly with the drug being antagonized to remove it or to prevent it from reaching its target. A chemical antagonist does not depend on interaction with the agonist's receptor (although such interaction may occur).

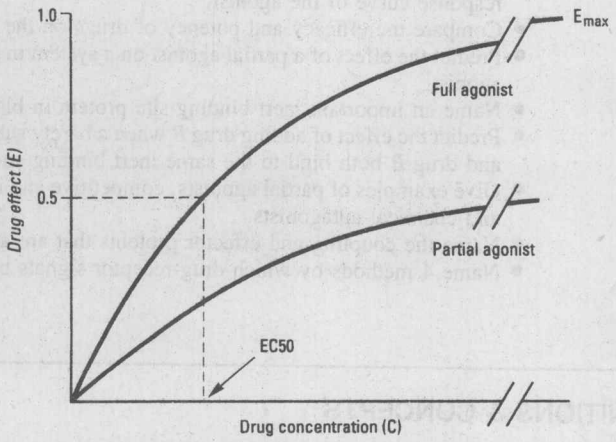

Figure 2–1. Relation between drug concentration and drug effect. The concentration at which effect is half-maximal is denoted EC50. If *receptor-bound* drug is plotted against drug concentration, a similar curve is obtained, and the concentration at which 50% of the receptors are associated with drug is denoted K_D. (Modified and reproduced, with permission, from Katzung BG [editor]: *Basic & Clinical Pharmacology*, 4th ed. Appleton & Lange, 1989).

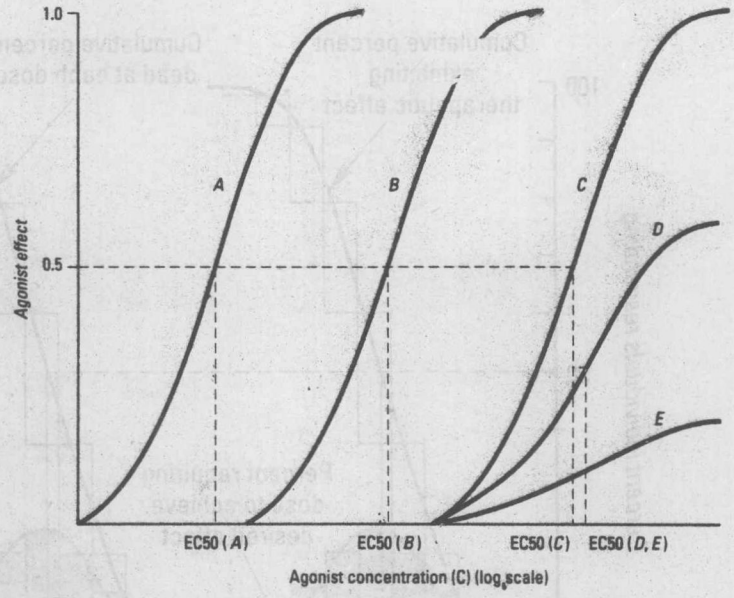

Figure 2–2. Agonist dose-response curves in the presence of competitive and noncompetitive antagonists. Note the use of a logarithmic scale for drug concentration. A competitive antagonist has an effect illustrated by curves *A*, *B*, and *C*. A noncompetitive antagonist shifts the curves downward (curves *D* and *E*). (Modified and reproduced, with permission, from Katzung BG [editor]: *Basic & Clinical Pharmacology*, 4th ed. Appleton & Lange, 1989.)

H. Efficacy: This refers to the maximum effect that a drug can produce, regardless of dose. Determined by the nature of the receptor and its associated effector system, efficacy can be measured only with a graded dose-response curve (Fig 2–1).

I. Potency: This denotes the amount of a drug needed to produce a given effect (usually 50% of the maximum effect). Potency is determined by the affinity of the receptor for the drug. ED50, TD50, and LD50 are typical potency measurements (effective, toxic, and lethal doses, respectively, in 50% of a population). Potency can be determined from either graded or quantal dose-response curves (eg, Figs 2–1, 2–3), but the numbers obtained are not identical.

J. Graded Dose-Response Relationships: When the response of a particular system (isolated tissue, animal, or patient) is measured against increasing concentrations of a drug, the graph of the response versus the drug concentration or dose is called a graded dose-response curve (Fig 2–1). In the presence of a competitive antagonist, the log dose versus response curve is shifted to higher doses (ie, horizontally on the dose axis) but still reaches the same maximum effect. In contrast, an irreversible antagonist causes a downward shift of the maximum, with no shift of the curve on the dose axis unless spare receptors are present (Fig 2–2).

K. Quantal Dose-Response Relationships: When the doses required to produce a specified response are determined in each member of a large population, the quantal dose-response relationship is defined (Fig 2–3). When plotted as the fraction of the population that responds at each dose level versus the log of the dose administered, a cumulative quantal dose-response curve, usually sigmoid in shape, is defined. The median effective (ED50), median toxic (TD50), and median lethal doses (LD50) can be extracted from such data.

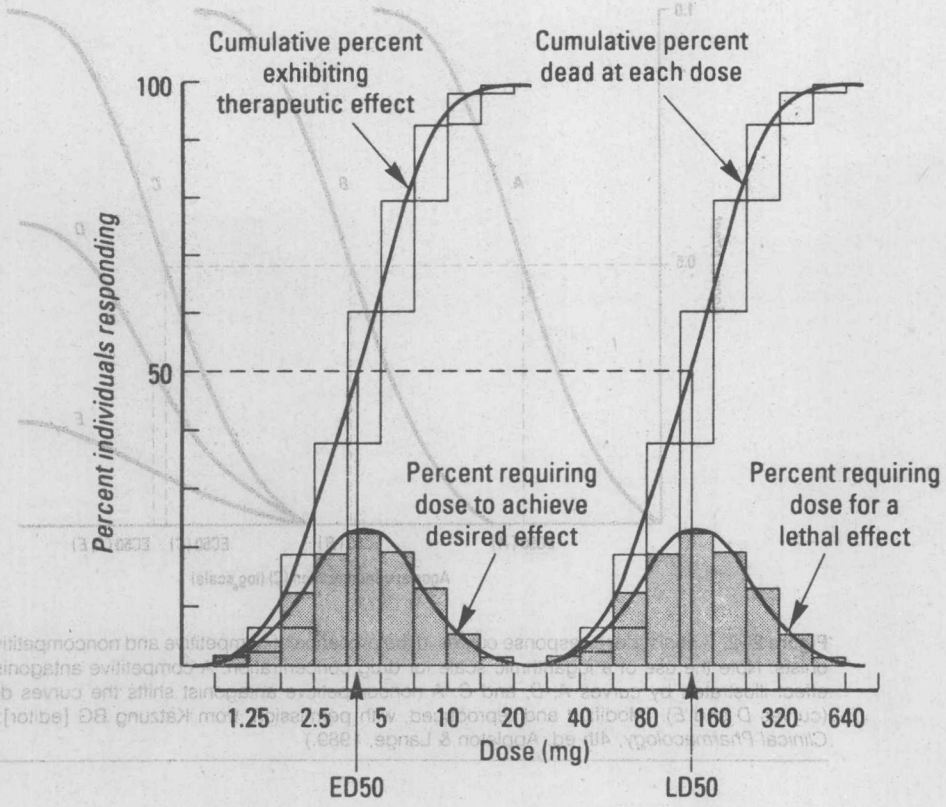

Figure 2–3. Quantal dose-effect plots. Shaded boxes (and the accompanying curves) indicate the frequency distribution of doses of drug required to produce a specified effect—ie, the percentage of animals that required a particular dose to exhibit the effect. The open boxes (and corresponding curves) indicate the cumulative frequency distribution of responses, which are lognormally distributed. (Reproduced, with permission, from Katzung BG [editor]: *Basic & Clinical Pharmacology*, 4th ed. Appleton & Lange, 1989.)

L. Signaling Mechanisms: Once an agonist drug has bound to its receptor, some effector mechanism is activated. For many useful drugs, the effector mechanism is located inside the cell or modifies some intracellular process. Four major types of transmembrane signaling mechanisms for drugs have been defined:

(1) Lipid-soluble drugs (eg, steroid hormones) can cross the membrane and combine with an intracellular receptor.

(2) Ion channel-regulating drugs (eg, acetylcholine at the nicotinic receptor) may directly regulate the opening of an ion channel.

(3) Enzyme-regulating drugs (eg, insulin) may combine with the extracellular portion of membrane-spanning enzymes and modify their intracellular activity.

(4) Drugs may bind to receptors that are linked by *coupling proteins* to intracellular effectors. The best defined examples are the sympathomimetic drugs, which activate or inhibit adenylate (adenylyl) cyclase.

(a) Activation is brought about by drugs that bind to beta-adrenoceptors; the drug-receptor interaction is coupled to the effector (adenylate cyclase) by a stimulatory coupling protein, G_s.

(b) Inhibition is accomplished by binding of drug to alpha-adrenoceptors; this interaction is coupled to adenylate cyclase by another G protein, G_i.

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