

Katzung's Basic and Clinical Pharmacology 16th Edition PDF

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Todd W. Vanderah



KATZUNG'S  
**BASIC & CLINICAL**  
**PHARMACOLOGY**

16th Edition

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## Preface

The 16th edition of *Basic & Clinical Pharmacology* will recognize Dr. Bertram Katzung's legacy of contribution to this book by retitling the book as *Katzung's Basic & Clinical Pharmacology* and his mentorship of Dr. Todd W. Vanderah as editor for this edition. This edition continues the extensive use of full-color illustrations and expanded coverage of transporters, pharmacogenomics, and new drugs of all types emphasized in prior editions. The 16th edition also reflects the major expansion of large-molecule drugs in the pharmacopeia, with numerous new monoclonal antibodies and other biologic agents. Case studies accompany most chapters, and answers to questions posed in the case studies appear at the end of each chapter. The book is designed to provide a comprehensive, authoritative, and readable pharmacology textbook for students in the health sciences.

This edition continues the sequence used in many pharmacology courses and in integrated curricula: basic principles of drug discovery, pharmacodynamics, pharmacokinetics, and pharmacogenomics; autonomic drugs; cardiovascular-renal drugs; drugs with important actions on smooth muscle; central nervous system drugs; drugs used to treat inflammation, gout, and diseases of the blood; endocrine drugs; chemotherapeutic drugs; toxicology; and special topics. This sequence builds new information on a foundation of information already assimilated. For example, early presentation of autonomic nervous system pharmacology allows students to integrate the physiology and neuroscience they have learned elsewhere with the pharmacology they are learning and prepares them to understand the autonomic effects of other drugs. This is especially important for the cardiovascular and central nervous system drug groups. However, chapters can be used equally well in courses and curricula that present these topics in a different sequence. Within each chapter, emphasis is placed on discussion of drug groups and prototypes rather than offering repetitive detail about individual drugs. Selection of the subject matter and the order of its presentation are based on the accumulated experience of teaching this material to thousands of medical, pharmacy, dental, podiatry, nursing, and other health science students.

Health science curricula now place more emphasis on the clinical applications of therapeutic measures. Major features that make this book particularly useful in such curricula include sections that specifically address the clinical choice and use of drugs in patients and the monitoring of their effects—in other words, *clinical pharmacology* is an integral part of this text. Lists of the trade and generic names of commercial preparations available are provided at the end of each chapter for easy reference by the house officer or practitioner evaluating a patient's drug list or writing a prescription.

The 16th edition includes the novel medications that were quickly designed to prevent and overcome COVID-19 with emphasis on the importance of vaccines and antiviral drugs in pharmacology and clinical medicine.

### Significant revisions in this edition include:

- Major revisions of the chapters on immunopharmacology; antiseizure, antipsychotic, antidepressant, antidiabetic, anti-inflammatory, and antiviral drugs; prostaglandins; and central nervous system neurotransmitters. Major additions on the treatment of COVID have been added in [Chapter 49](#).
- Continued expansion of the coverage of general concepts relating to newly discovered receptors, receptor mechanisms, and drug transporters.
- Descriptions of important new drugs, especially biologicals, released through January 2022.
- Revised illustrations in full color that provide significantly more information about drug mechanisms and effects and help to clarify important concepts.

An important related educational resource is *Katzung's Pharmacology: Examination & Board Review*, 14th edition (Marieke Kruidering-Hall, Rupa L. Tuan, Todd W. Vanderah, Bertram G. Katzung, eds, McGraw Hill, 2024). This book provides a succinct review of pharmacology with almost 1000 sample examination questions and answers. It is especially helpful to students preparing for board-type examinations. A more highly condensed source of information suitable for review purposes is *USMLE Road Map: Pharmacology*, 2nd edition (Katzung BG, Trevor AJ: McGraw Hill, 2006). An extremely useful manual of toxicity due to drugs and other products is *Poisoning & Drug Overdose*, by Olson KR, ed; 8th edition, McGraw Hill, 2022.

The 16th edition marks the 42nd year of publication of *Basic & Clinical Pharmacology*. The widespread adoption of the first fifteen editions indicates that this book fills an important need. We believe that the 16th edition will satisfy this need even more successfully. Chinese, Croatian, Czech, French, Georgian, Indonesian, Italian, Japanese, Korean, Lithuanian, Portuguese, Spanish, Turkish, and Ukrainian translations of various editions are available. The publisher may be contacted for further information.

I wish to acknowledge the prior and continuing efforts of my contributing authors and the major contributions of the staff at Lange Medical Publications, Appleton & Lange, and McGraw Hill, and of our copy editor for this edition, Greg Feldman. I also wish to thank Tasneem Kauser for her contributions.

Suggestions and comments about *Katzung's Basic & Clinical Pharmacology* are always welcome. They may be sent to me in care of the publisher.

*Todd W. Vanderah, PhD  
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## Chapter 1: Introduction: The Nature of Drugs & Drug Development & Regulation

Todd W. Vanderah; Bertram G. Katzung

### CASE STUDY

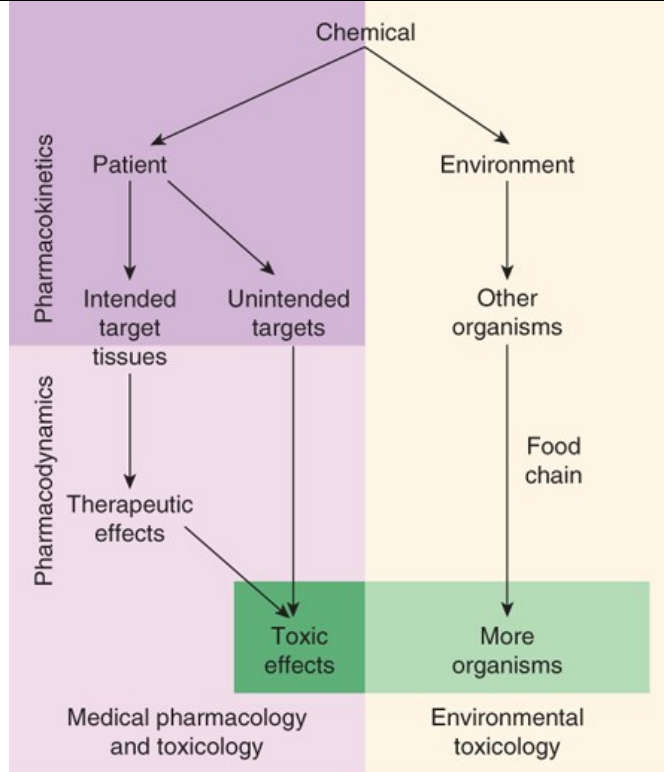
#### CASE STUDY

A 78-year-old woman is brought to the hospital because of suspected **aspirin** overdose. She has taken **aspirin** for joint pain for many years without incident, but during the past year, she has exhibited signs of cognitive decline. Her caregiver finds her confused, hyperventilating, and vomiting. The caregiver finds an empty bottle of **aspirin** tablets and calls 9-1-1. In the emergency department, samples of venous and arterial blood are obtained while the airway, breathing, and circulation are evaluated. An intravenous (IV) drip is started, and gastrointestinal decontamination is started. After blood gas results are reported, sodium bicarbonate is administered via the IV. What is the purpose of the sodium bicarbonate?

**Pharmacology** can be defined as the study of substances that interact with living systems through chemical processes. These interactions usually occur by binding of the substance to regulatory molecules and activating or inhibiting normal body processes. These substances may be chemicals administered to achieve a beneficial therapeutic effect on some process within the patient or for their toxic effects on regulatory processes in parasites infecting the patient. Such deliberate therapeutic applications may be considered the proper role of **medical pharmacology**, which is often defined as the science of substances used to prevent, diagnose, and treat disease. **Toxicology** is the branch of pharmacology that deals with the undesirable effects of chemicals on living systems, from individual cells to humans to complex ecosystems (Figure 1-1). The nature of drugs—their physical properties and their interactions with biological systems—is discussed in part I of this chapter.

#### FIGURE 1-1

Major areas of study in pharmacology. The actions of chemicals can be divided into two large domains. The first (*left side*) is that of medical pharmacology and toxicology, which is aimed at understanding the actions of drugs as chemicals on individual organisms, especially humans and domestic animals. Both beneficial and toxic effects are included. Pharmacokinetics deals with the absorption, distribution, and elimination of drugs. Pharmacodynamics concerns the actions of the chemical on the organism. The second domain (*right side*) is that of environmental toxicology, which is concerned with the effects of chemicals on all organisms and their survival in groups and as species.



Source: Todd W. Vanderah:  
Basic & Clinical Pharmacology, Sixteenth Edition  
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New drugs are added every year; they are needed for several reasons including: (1) increasing resistance by bacteria and other parasites; (2) discovery of new target processes in diseases that have not been adequately treated; and (3) recognition of new diseases. Furthermore, a dramatic increase has occurred in the number of *large molecule* drugs (especially antibodies) approved during the last two decades. The development of new drugs and their regulation by government agencies are discussed in part II.

## THE HISTORY OF PHARMACOLOGY

Prehistoric people undoubtedly recognized the beneficial or toxic effects of many plant and animal materials. Early written records list remedies of many types, including a few that are still recognized as useful drugs today. Most, however, were worthless or actually harmful. Beginning about 1500 years ago, sporadic attempts were made to introduce rational methods into medicine, but none was successful owing to the dominance of systems of thought (“schools”) that purported to explain all of biology and disease without the need for experimentation and observation. These schools promulgated bizarre notions such as the idea that disease was caused by excesses of bile or blood in the body, that wounds could be healed by applying a salve to the weapon that caused the wound, and so on.

Around the end of the 17th century, concepts based on observation and experimentation began to replace theorizing in physiology and clinical medicine. As the value of these methods in the study of disease became clear, physicians in Great Britain and on the Continent began to apply them systematically to the effects of traditional drugs used in their own practices. Thus, **materia medica**—the science of drug preparation and the medical uses of drugs—began to develop as the precursor to pharmacology. However, any real understanding of the mechanisms of action of drugs was prevented by the absence of methods for purifying active agents from the crude materials that were available and—even more—by the lack of methods for testing hypotheses about the nature of drug actions.

In the late 18th and early 19th centuries, François Magendie and his student Claude Bernard began to develop the methods of **experimental physiology** and **pharmacology**. Advances in chemistry and the further development of physiology in the 18th, 19th, and early 20th centuries laid the foundation needed for understanding how drugs work at the organ and cellular levels. Paradoxically, real advances in basic pharmacology during this time were accompanied by an outburst of unscientific claims by manufacturers and marketers of worthless “patent medicines.” Not until the concepts of rational therapeutics, especially that of the **controlled clinical trial**, were reintroduced into medicine—only about 60 years ago—did it become

possible to adequately evaluate therapeutic claims.

Around the 1940s and 1950s, a major expansion of research efforts in all areas of biology began. As new concepts and new techniques were introduced, information accumulated about drug action and the biologic substrate of that action, the **drug receptor**. During the last 60 years, many fundamentally new drug groups and new members of old groups have been introduced. The last three decades have seen an even more rapid growth of information and understanding of the molecular basis for drug action. The molecular mechanisms of action of many drugs have now been identified, and numerous receptors have been isolated, structurally characterized, and cloned. In fact, the use of receptor identification methods (described in [Chapter 2](#)) has led to the discovery of many *orphan* receptors—receptors for which no ligand has been discovered and whose function can only be guessed. Studies of the local molecular environment of receptors have shown that receptors and effectors do not function in isolation; they are strongly influenced by other receptors and by companion regulatory proteins. Most recently, it has become clear that gravitational change, radiation, and other aspects of space *outside* the Earth’s environment require the development of *space medicine*. This has opened another important area for the future of pharmacology. One result of these discoveries is the confirmation that pharmacology represents an area where anatomy, biochemistry, genetics, physiology, pathology, clinical medicine, and the environment meet. Many problems that the health practitioner confronts can now be corrected or mitigated using pharmacologic tools.

**Pharmacogenomics**—the relation of the individual’s genetic makeup to his or her response to specific drugs—is becoming an important part of therapeutics (see [Chapter 5](#)). Decoding of the genomes of many species—from bacteria to humans—has led to the recognition of unsuspected relationships between receptor families and the ways that receptor proteins have evolved. Furthermore, discovery of regulatory functions exerted by the neighbors of chromosomes and the *noncoding* regions of DNA on the expression of exons has opened a new area of possible manipulation of the genes—epigenetics—that control pharmacologic responses.

The discovery that small segments of RNA can interfere with protein synthesis with extreme selectivity has led to investigation of **small interfering RNAs (siRNAs)** and **micro-RNAs (miRNAs)** as therapeutic agents. Similarly, short nucleotide chains called **antisense oligonucleotides (ANOs)**, synthesized to be complementary to natural RNA or DNA, can interfere with the readout of genes and the transcription of RNA. Recently, the development of mRNA vaccines has led to new medications by activating one’s own immune system to recognize and fight off viruses. New, efficient methods of DNA editing have made possible the modification of genes that encode proteins that are critical to biological function, representing a transformative means of generating medicines. Finally, development in the production of selective monoclonal antibodies to target selective proteins has led to a dramatic increase in *large molecule* therapeutics in the last 20 years ([Table 1–1](#)).

TABLE 1–1

**Development of large molecule therapeutic agents as a percentage of all new drug approvals, 2000–2020.**

Year	Total New Drug Approvals	New Protein Drugs (~% of new drug approvals)	New MABs (~% of new drug approvals)
2000	63	3 (5%)	1 (2%)
2008	34	5 (15%)	1 (3%)
2010	49	8 (16%)	4 (8%)
2015	69	13 (19%)	9 (13%)
2017	63	10 (16%)	9 (14%)
2020	61	? (16%)	10 (16%)

MABs, monoclonal antibodies.

Unfortunately, the medication-consuming public is still exposed to vast amounts of inaccurate or unscientific information regarding the pharmacologic effects of chemicals. This results in the irrational use of innumerable expensive, ineffective, and sometimes harmful remedies and the

growth of a huge “alternative health care” industry. Furthermore, manipulation of the legislative process in the United States has allowed many substances promoted for health—but not promoted specifically as “drugs”—to avoid meeting the Food and Drug Administration (FDA) standards described in the second part of this chapter. Conversely, lack of understanding of basic scientific principles in biology and statistics and the absence of critical thinking about public health issues have led to rejection of medical science, including vaccines, by a segment of the public and a tendency to assume that all adverse drug effects are the result of malpractice.

General principles that the student should remember are (1) that *all* substances can under certain circumstances be toxic; (2) that the chemicals in botanicals (herbs and plant extracts, “nutraceuticals”) are no different from chemicals in manufactured drugs except for the much greater proportion of impurities in botanicals; and (3) that all dietary supplements and all therapies promoted as health-enhancing should meet the same standards of efficacy and safety as conventional drugs and medical therapies. That is, there should be no artificial separation between scientific medicine and “alternative” or “complementary” medicine. Ideally, all nutritional and botanical substances should be tested by the same types of randomized controlled trials (RCTs) as synthetic compounds.

## GENERAL PRINCIPLES OF PHARMACOLOGY

### THE NATURE OF DRUGS

In the most general sense, a drug may be defined as any substance that brings about a change in biologic function through its chemical actions. In most cases, the drug molecule interacts as an **agonist** (activator) or **antagonist** (inhibitor) with a specific target molecule that plays a regulatory role in the biologic system. This target molecule is called a **receptor**. Some of the new large molecule drugs (**biologicals**) act like receptors themselves and bind endogenous molecules. The nature of receptors is discussed more fully in [Chapter 2](#). In a very small number of cases, drugs known as **chemical antagonists** may interact directly with other drugs, whereas a few drugs (**osmotic agents**) interact almost exclusively with water molecules. Drugs may be synthesized within the body (eg, **hormones**) or may be chemicals *not* synthesized in the patient’s body (ie, **xenobiotics**). **Poisons** are drugs that have almost exclusively harmful effects. However, Paracelsus (1493–1541) famously stated that “the dose makes the poison,” meaning that any substance can be harmful if taken in the wrong dosage. **Toxins** are usually defined as poisons of biologic origin, ie, synthesized by plants or animals, in contrast to inorganic poisons such as lead and arsenic.

#### The Physical Nature of Drugs

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

Drugs may be solid at room temperature (eg, [aspirin](#), [atropine](#)), liquid (eg, [nicotine](#), ethanol), or gaseous (eg, nitrous oxide, [isoflurane](#), xenon). These factors often determine the best route of administration. The most common routes of administration are described in [Chapter 3](#), [Table 3–3](#). The various classes of organic compounds—carbohydrates, proteins, lipids, and smaller molecules—are all represented in pharmacology. As noted above, many proteins and some new mRNA vaccines have been approved while some oligonucleotides have also received approval for use depending on the country’s regulation agencies.

A number of inorganic elements, eg, [fluoride](#), [lithium](#), iron, and heavy metals, are both useful and dangerous drugs. Many organic drugs are weak acids or bases. This fact has important implications for the way they are handled by the body, because pH differences in the various compartments of the body may alter the degree of ionization of weak acids and bases (see text that follows).

#### Drug Size

The molecular size of drugs varies from very small ([lithium ion](#), molecular weight [MW] 7) to very large (eg, [alteplase](#) [t-PA], a protein of MW 59,050). Many antibodies are even larger; eg, [erenumab](#), an antibody used in the management of migraine, has a MW of more than 145,000. However, most drugs have molecular weights between 100 and 1000. The lower limit of this narrow range is probably set by the requirements for specificity of action. To have a good “fit” to only one type of receptor, a drug molecule must be sufficiently unique in shape, charge, and other properties to prevent its binding to other receptors. To achieve such selective binding, it appears that a molecule should in most cases be at least 100 MW units in size. The

upper limit in molecular weight is determined primarily by the requirement that most drugs must be able to move within the body (eg, from the site of administration to the site of action and then to the site of elimination). Drugs much larger than MW 1000 do not diffuse readily between compartments of the body (discussed under Permeation, in following text). Therefore, very large drugs (usually proteins) must often be administered directly into the compartment where they have their effect. In the case of [alteplase](#), a clot-dissolving enzyme, it is administered directly into the vascular compartment by intravenous or intra-arterial infusion.

## Drug Reactivity & Drug-Receptor Bonds

Drugs interact with receptors by means of chemical forces or bonds. These are of three major types: **covalent**, **electrostatic**, and **hydrophobic**. Covalent bonds are very strong and in many cases not reversible under biologic conditions. Thus, the covalent bond formed between the acetyl group of acetylsalicylic acid ([aspirin](#)) and cyclooxygenase, its enzyme target in platelets, is not readily broken. The platelet aggregation-blocking effect of [aspirin](#) lasts long (days) after free acetylsalicylic acid has disappeared from the bloodstream (about 15 minutes) and is reversed only by the synthesis of new enzyme in new platelets, a process that takes several days. Other examples of highly reactive, covalent bond-forming drugs include the DNA-alkylating agents used in cancer chemotherapy to disrupt cell division in the tumor.

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

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

The specific nature of a particular drug-receptor bond is of less practical importance than the fact that drugs that bind through weak bonds to their receptors are generally more selective than drugs that bind by means of very strong bonds. This is because weak bonds require a very precise fit of the drug to its receptor if an interaction is to occur. Only a few receptor types are likely to provide such a precise fit for a particular drug structure. Thus, if we wished to design a highly selective drug for a particular receptor, we would avoid highly reactive molecules that form covalent bonds and instead choose a molecule that forms weaker bonds.

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

## Drug Shape

The shape of a drug molecule must be such as to permit binding to its target site via the bonds just described. Optimally, the drug’s shape is complementary to that of the target site (usually a receptor) in the same way that a key is complementary to a lock. Furthermore, the phenomenon of **chirality (stereoisomerism)** is so common in biology that more than half of all useful drugs are chiral molecules; that is, they can exist as enantiomeric pairs. Drugs with two asymmetric centers have four diastereomers, eg, [ephedrine](#), a sympathomimetic drug. In most cases, one of these enantiomers is much more potent than its mirror image enantiomer, reflecting a better fit to the receptor molecule. If one imagines the receptor site to be like a glove into which the drug molecule must fit to bring about its effect, it is clear why a “left-oriented” drug is more effective in binding to a left-hand receptor than its “right-oriented” enantiomer.

The more active enantiomer at one type of receptor site may not be more active at another receptor type, eg, a type that may be responsible for some other effect. For example, [carvedilol](#), a drug that interacts with adrenoceptors, has a single chiral center and thus two enantiomers ([Table 1-2](#)). One of these enantiomers, the (*S*)(-) isomer, is a potent  $\beta$ -receptor blocker. The (*R*)(+) isomer is 100-fold weaker at the  $\beta$  receptor. However, the isomers are approximately equipotent as  $\alpha$ -receptor blockers. [Ketamine](#), a chiral molecule with two isomers, was introduced as an anesthetic. When administered as an anesthetic, the racemic mixture is administered intravenously. In contrast, the (*S*) enantiomer has recently been approved for use in nasal spray form as a rapid-acting antidepressant.

**Dissociation constants ( $K_d$ ) of the enantiomers and racemate of carvedilol.**

Form of Carvedilol	$\alpha$ Receptors ( $K_d$ , nmol/L <sup>1</sup> )	$\beta$ Receptors ( $K_d$ , nmol/L)
(R)(+) enantiomer	14	45
(S)(-) enantiomer	16	0.4
(R,S)(±) enantiomers	11	0.9

<sup>1</sup>The  $K_d$  is the concentration for 50% saturation of the receptors and is inversely proportionate to the affinity of the drug for the receptors.

Data from Ruffolo RR Jr, Gellai M, Hieble JP, et al: The Pharmacology of carvedilol. *Eur J Clin Pharmacol* 1990;38S2:S82-88.

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

Unfortunately, most studies of clinical efficacy and drug elimination in humans have been carried out with racemic mixtures of drugs rather than with the separate enantiomers. At present, less than half of the chiral drugs used clinically are marketed as the active isomer—the rest are available only as racemic mixtures. As a result, a majority of patients receive drug doses of which 50% is less active or inactive. A few drugs are currently available in both the racemic and the pure, active isomer forms. However, proof that administration of the pure, active enantiomer decreases adverse effects relative to those produced by racemic formulations has not been established.

### Rational Drug Design

Rational design of drugs implies the ability to predict the appropriate molecular structure of a drug on the basis of information about its biologic receptor. Until recently, no receptor was known in sufficient detail to permit such drug design. Instead, drugs were developed through random testing of chemicals or modification of drugs already known to have some effect. However, the characterization of many receptors during the past three decades has changed this picture. A few drugs now in use were developed through molecular design based on knowledge of the three-dimensional structure of the receptor site. Computer programs are now available that can iteratively optimize drug structures to fit known receptors. As more becomes known about receptor structure, rational drug design will become more common.

### Receptor Nomenclature

The spectacular success of newer, more efficient ways to identify and characterize receptors (see [Chapter 2](#)) has resulted in a variety of differing, and sometimes confusing, systems for naming them. This in turn has led to a number of suggestions regarding more rational methods of naming receptors. The interested reader is referred for details to the efforts of the International Union of Pharmacology (IUPHAR) Committee on Receptor Nomenclature and Drug Classification (reported in various issues of *Pharmacological Reviews* and elsewhere) and to Alexander SP et al: The Concise guide to pharmacology 2017/18: Overview. *Br J Pharmacol* 2017;174:S1. The chapters in this book mainly use these sources for naming receptors.

## DRUG-BODY INTERACTIONS

The interactions between a drug and the body are conveniently divided into two classes. The actions of the drug on the body are termed **pharmacodynamic** processes (see [Figure 1-1](#)); the principles of pharmacodynamics are presented in greater detail in [Chapter 2](#). These properties determine the group in which the drug is classified, and they play the major role in deciding whether that group is appropriate therapy for a particular symptom or disease. The actions of the body on the drug are called **pharmacokinetic** processes and are described in [Chapters 3](#) and [4](#). Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient, eg, a patient with heart failure who also has impaired renal function. The following paragraphs provide a brief introduction to pharmacodynamics and pharmacokinetics.

## Pharmacodynamic Principles

Most drugs must bind to a receptor to bring about an effect. However, at the cellular level, drug binding is only the first in a sequence of possible steps:

- Drug (D) + receptor-effector (R) → drug-receptor-effector complex → effect
- D + R → drug-receptor complex → effector molecule → effect
- D + R → D-R complex → activation of coupling molecule → effector molecule → effect
- Inhibition of metabolism of endogenous activator → increased activator action on an effector molecule → increased effect

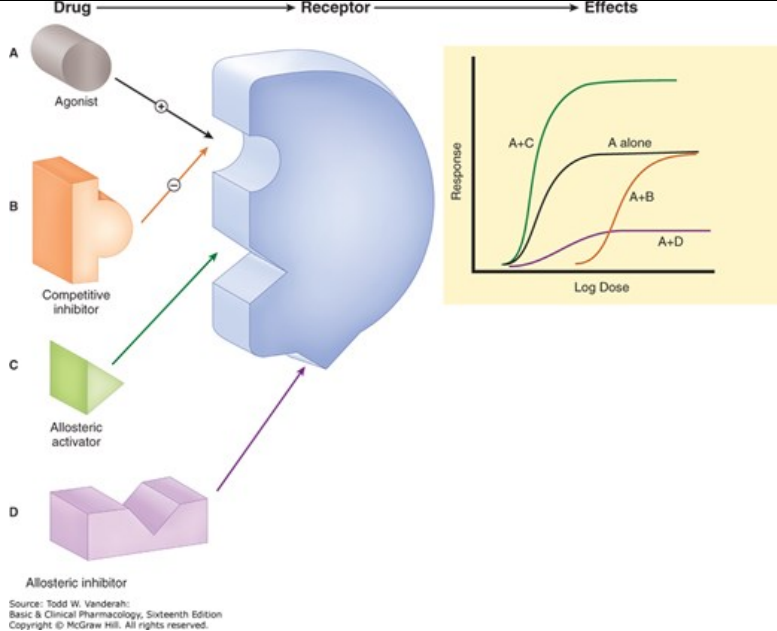
Note that the final change in function is accomplished by an **effector** mechanism. The effector may be part of the receptor molecule or may be a separate molecule. A very large number of receptors communicate with their effectors through coupling molecules, as described in [Chapter 2](#).

### A. Types of Drug-Receptor Interactions

**Agonist** drugs bind to and *activate* the receptor in some fashion, which directly or indirectly brings about the effect ([Figure 1-2A](#)). Receptor activation involves a change in conformation in the cases that have been studied at the molecular structure level. Some receptors incorporate effector machinery in the same molecule, so that drug binding brings about the effect directly, eg, opening of an ion channel or activation of enzyme activity. Other receptors are linked through one or more intervening coupling molecules to a separate effector molecule. The major types of drug-receptor-effector coupling systems are discussed in [Chapter 2](#). **Pharmacologic antagonist** drugs, by binding to a receptor, compete with and prevent binding by other molecules. For example, [acetylcholine](#) receptor blockers such as [atropine](#) are antagonists because they prevent access of [acetylcholine](#) and similar agonist drugs to the [acetylcholine](#) receptor site and they stabilize the receptor in its inactive state (or some state other than the acetylcholine-activated state). These agents reduce the effects of [acetylcholine](#) and similar molecules in the body ([Figure 1-2B](#)), but their action can be overcome by increasing the dosage of agonist. Some antagonists bind very tightly to the receptor site in an irreversible or pseudoirreversible fashion and cannot be displaced by increasing the agonist concentration. Drugs that bind to the same receptor molecule but do not prevent binding of the agonist are said to act **allosterically** and may enhance ([Figure 1-2C](#)) or inhibit ([Figure 1-2D](#)) the action of the agonist molecule. Allosteric inhibition is not usually overcome by increasing the dose of agonist.

#### FIGURE 1-2

Drugs may interact with receptors in several ways. The effects resulting from these interactions are diagrammed in the dose-response curves at the right. Drugs that alter the agonist (**A**) response may activate the agonist binding site, compete with the agonist (competitive inhibitors, **B**), or act at separate (allosteric) sites, increasing (**C**) or decreasing (**D**) the response to the agonist. Allosteric activators (**C**) may increase the efficacy of the agonist or its binding affinity. The curve shown reflects an increase in efficacy; an increase in affinity would result in a leftward shift of the curve.



### B. Agonists That Inhibit Their Binding Molecules

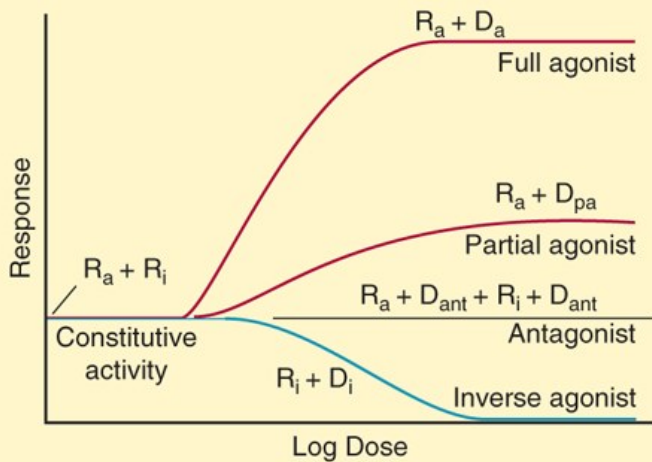
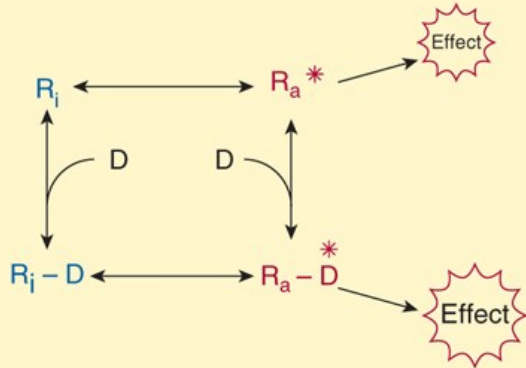
Some drugs mimic agonist drugs by inhibiting the molecules responsible for terminating the action of an endogenous agonist. For example, acetylcholinesterase *inhibitors*, by slowing the destruction of endogenous **acetylcholine**, cause cholinomimetic effects that closely resemble the actions of cholinergic *agonist* molecules even though cholinesterase inhibitors do not bind or only incidentally bind to cholinergic receptors (see [Chapter 7](#)). Because they amplify the effects of physiologically released endogenous agonist ligands, their effects are sometimes more selective and less toxic than those of exogenous agonists.

### C. Agonists, Partial Agonists, and Inverse Agonists

[Figure 1-3](#) describes a useful model of drug-receptor interactions. As indicated, the receptor is postulated to exist partially in the inactive, nonfunctional form ( $R_i$ ) and partially in the activated form ( $R_a$ ). Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the  $R_a$  form some of the time and may produce the same physiologic effect as agonist-induced activity. This effect, occurring in the absence of agonist, is termed **constitutive** or **basal activity**. Agonists have a much higher affinity for the  $R_a$  configuration and stabilize it, so that a large percentage of the total pool resides in the  $R_a$ -D fraction and a large effect is produced. The recognition of constitutive activity may depend on the receptor density, the concentration of coupling molecules (if a coupled system), and the number of effectors in the system.

FIGURE 1-3

A model of drug-receptor interaction. The hypothetical receptor is able to assume two conformations. In the  $R_i$  conformation, it is inactive and produces no effect, even when combined with a drug molecule. In the  $R_a$  conformation, the receptor can activate downstream mechanisms that produce a small observable effect, even in the absence of drug (constitutive activity). In the absence of drugs, the two isoforms are in equilibrium, and the  $R_i$  form is favored. Conventional full agonist drugs have a much higher affinity for the  $R_a$  conformation, and mass action thus favors the formation of the  $R_a$ -D complex with a much larger observed effect. Partial agonists have an intermediate affinity for both  $R_i$  and  $R_a$  forms. Conventional antagonists, according to this hypothesis, have equal affinity for both receptor forms and maintain the same level of constitutive activity. Inverse agonists, on the other hand, have a much higher affinity for the  $R_i$  form, reduce constitutive activity, and may produce a contrasting physiologic result.



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Many agonist drugs, when administered at concentrations sufficient to saturate the receptor pool, can activate their receptor-effector systems to the maximum extent of which the system is capable; that is, they cause a shift of almost all of the receptor pool to the  $R_a$ -D pool. Such drugs are termed **full agonists**. Other drugs, called **partial agonists**, bind to the same receptors and activate them in the same way but do not evoke as great a response, no matter how high the concentration. In the model in Figure 1-3, partial agonists do not stabilize the  $R_a$  configuration as fully as full agonists, so that a significant fraction of receptors exists in the  $R_i$ -D pool. Such drugs are said to have low **intrinsic efficacy**. Because they occupy the same receptor site, partial agonists can also prevent access by full agonists. Thus, **pindolol**, a  $\beta$ -adrenoceptor partial agonist, may act either as an agonist (if no full agonist is present) or as an antagonist (if a full agonist such as **epinephrine** is present). (See Chapter 2.) Intrinsic efficacy is independent of affinity (as usually measured) for the receptor.

In the same model, conventional antagonist action can be explained as fixing the fractions of drug-bound  $R_i$  and  $R_a$  in the same relative amounts as in the absence of any drug. In this situation, no change in activity will be observed, so the drug will appear to be without effect. However, the presence of the antagonist at the receptor site will block access of agonists to the receptor and prevent the usual agonist effect. Such blocking action can be termed **neutral antagonism**.

What will happen if a drug has a much stronger affinity for the  $R_i$  than for the  $R_a$  state and stabilizes a large fraction in the  $R_i$ -D pool? In this scenario the drug will reduce any constitutive activity, thus resulting in effects that are the opposite of the effects produced by conventional agonists at that receptor. Such drugs are termed **inverse agonists** (see Figure 1-3). One of the best documented examples of such a system is the  $\gamma$ -aminobutyric acid ( $GABA_A$ ) receptor-effector (a chloride channel) in the nervous system. This receptor is activated by the endogenous transmitter GABA and causes inhibition of postsynaptic cells. Conventional exogenous agonists such as benzodiazepines also facilitate the receptor-effector system and enhance GABA-like chloride entry into cells with sedation as the therapeutic result. This sedation can be reversed by conventional neutral antagonists such as

**flumazenil**. Inverse agonists of this receptor system cause anxiety and agitation, the inverse of sedation (see [Chapter 22](#)). Similar inverse agonists have been found for  $\beta$  adrenoceptors, histamine  $H_1$  and  $H_2$  receptors, and several other receptor systems.

#### D. Duration of Drug Action

Termination of drug action can result from several processes. In some cases, the effect lasts only as long as the drug occupies the receptor, and dissociation of drug from the receptor automatically terminates the effect. In many cases, however, the action may persist after the drug has dissociated because, for example, some coupling molecule is still present in activated form. In the case of drugs that bind covalently to the receptor site, the effect may persist until the drug-receptor complex is destroyed and new receptors or enzymes are synthesized, as described previously for [aspirin](#). In addition, many receptor-effector systems incorporate desensitization mechanisms for preventing excessive activation when agonist molecules continue to be present for long periods. (See [Chapter 2](#) for additional details.)

#### E. Receptors and Inert Binding Sites

To function as a receptor, an endogenous molecule must first be **selective** in choosing ligands (drug molecules) to bind; and second, it must **change its function** upon binding in such a way that the function of the biologic system (cell, tissue, etc) is altered. The selectivity characteristic is required to avoid constant activation of the receptor by promiscuous binding of many different ligands. The ability to change function is clearly necessary if the ligand is to cause a pharmacologic effect. In some cases the function of the ligand may be to inhibit the endogenous actions of the receptor (antagonist and inverse agonist). The body contains a vast array of molecules that are capable of binding drugs, however, and not all of these endogenous molecules are regulatory molecules. Binding of a drug to a nonregulatory molecule such as plasma [albumin](#) will result in no detectable change in the function of the biologic system, so this endogenous molecule can be called an **inert binding site**. Such binding is not completely without significance, however, because it affects the distribution of drug within the body and determines the amount of free drug in the circulation. Both of these factors are of pharmacokinetic importance (see also [Chapter 3](#)).

### Pharmacokinetic Principles

In practical therapeutics, a drug should be able to reach its intended site of action after administration by some convenient route. In many cases, the active drug molecule is sufficiently lipid-soluble and stable to be given as such. In some cases, however, an inactive precursor chemical that is readily absorbed and distributed must be administered and then converted to the active drug by biologic processes—inside the body. Such a precursor chemical is called a **prodrug**.

In only a few situations is it possible to apply a drug directly to its target tissue, eg, by topical application of an anti-inflammatory agent to inflamed skin or mucous membrane. Most often, a drug is administered into one body compartment, eg, the gut, and must move to its site of action in another compartment, eg, the brain in the case of an antiseizure medication. This requires that the drug be **absorbed** into the blood from its site of administration and **distributed** to its site of action, **permeating** through the various barriers that separate these compartments. For a drug given orally to produce an effect in the central nervous system, these barriers include the tissues that make up the wall of the intestine, the walls of the capillaries that perfuse the gut, and the blood-brain barrier, the walls of the capillaries that perfuse the brain. Finally, after bringing about its effect, a drug should be **eliminated** at a reasonable rate by metabolic inactivation, by excretion from the body, or by a combination of these processes.

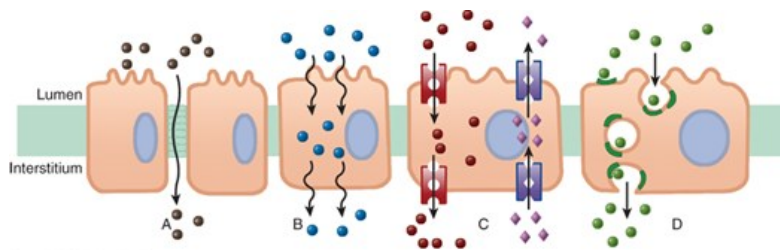
#### A. Permeation

Drug permeation proceeds by several mechanisms. Passive diffusion in an aqueous or lipid medium is common, but active processes play a role in the movement of many drugs, especially those whose molecules are too large to diffuse readily ([Figure 1-4](#)). Drug **vehicles** can be very important in facilitating transport and permeation, eg, by encapsulating the active agent in liposomes and in regulating release, as in slow release preparations. Newer methods of facilitating transport of drugs by coupling them to **nanoparticles** are under investigation.

#### FIGURE 1-4

Mechanisms of drug permeation. Drugs may diffuse passively through aqueous channels in the intercellular junctions (eg, tight junctions, **A**), or through lipid cell membranes (**B**). Drugs with the appropriate characteristics may be transported by carriers into or out of cells (**C**). Very impermeant drugs may also bind to cell surface receptors (dark binding sites), be engulfed by the cell membrane (endocytosis), and then be released inside the cell

or expelled via the membrane-limited vesicles out of the cell into the extracellular space (exocytosis, **D**).



### 1. Aqueous diffusion

Aqueous diffusion occurs within the larger aqueous compartments of the body (interstitial space, cytosol, etc) and across epithelial membrane tight junctions and the endothelial lining of blood vessels through aqueous pores that—in some tissues—permit the passage of molecules as large as MW 20,000–30,000.\* See [Figure 1–4A](#).

Aqueous diffusion of drug molecules is usually driven by the concentration gradient of the permeating drug, a downhill movement described by Fick's law (see below). Drug molecules that are bound to large plasma proteins (eg, [albumin](#)) do not permeate most vascular aqueous pores. If the drug is charged, its flux is also influenced by electrical fields (eg, the membrane potential and—in parts of the nephron—the transtubular potential).

### 2. Lipid diffusion

Lipid diffusion is the most important limiting factor for drug permeation because of the large number of lipid barriers that separate the compartments of the body. Because these lipid barriers separate aqueous compartments, the **lipid:aqueous partition coefficient** of a drug determines how readily the molecule moves between aqueous and lipid media. In the case of weak acids and weak bases (which gain or lose electrical charge-bearing protons, depending on the pH), the ability to move from aqueous to lipid or vice versa varies with the pH of the medium, because charged molecules attract water molecules. The ratio of lipid-soluble form to water-soluble form for a weak acid or weak base is expressed by the Henderson-Hasselbalch equation (described in the following text). See [Figure 1–4B](#).

### 3. Special carriers

Special carrier molecules exist for many substances that are important for cell function and are too large or too insoluble in lipid to diffuse passively through membranes, eg, peptides, amino acids, and glucose. These carriers bring about movement by active transport or facilitated diffusion and, unlike passive diffusion, are selective, saturable, and inhibitable. Because many drugs are or resemble such naturally occurring peptides, amino acids, or sugars, they can use these carriers to cross membranes. See [Figure 1–4C](#).

Many cells also contain less selective membrane carriers that are specialized for expelling foreign molecules. One large family of such transporters binds [adenosine](#) triphosphate (ATP) and is called the ABC (ATP-binding cassette) family. This family includes the **P-glycoprotein** or **multidrug resistance type 1 (MDR1) transporter** found in the brain, testes, and other tissues and in some drug-resistant neoplastic cells ([Table 1–3](#)). Similar transport molecules from the ABC family, the **multidrug resistance-associated protein (MRP)** transporters, play important roles in the excretion of some drugs or their metabolites into urine and bile and in the resistance of some tumors to chemotherapeutic drugs. Genomic variation in the expression of these transporters has a profound effect on sensitivity to these drugs (see [Chapter 5](#)). Several other transporter families have been identified that do not bind ATP but use ion gradients to drive transport. Some of these (the solute carrier [SLC] family) are particularly important in the uptake of neurotransmitters across nerve-ending membranes. The latter carriers are discussed in more detail in [Chapter 6](#).

**Some transport molecules important in pharmacology.**

Transporter	Physiologic Function	Pharmacologic Significance
NET	Norepinephrine reuptake from synapse	Target of cocaine and some tricyclic antidepressants
SERT	Serotonin reuptake from synapse	Target of selective serotonin reuptake inhibitors and some tricyclic antidepressants
VMAT	Transport of dopamine and norepinephrine into adrenergic vesicles in nerve endings	Target of reserpine and tetrabenazine
MDR1	Transport of many xenobiotics out of cells	Increased expression confers resistance to certain anticancer drugs; inhibition increases blood levels of digoxin
MRP1	Leukotriene secretion	Confers resistance to certain anticancer and antifungal drugs
OCT	Organic cationic compound uptake	Target for uptake of organic cationic compounds (acetylcholine, dopamine, norepinephrine, metformin, etc) into many tissues including the brain, liver, heart, kidney
OATP	Organic anionic and neutral compound uptake	Target for uptake of organic anionic compounds (prostaglandins, hormones, bile salts, statins, etc) into many tissues including the brain, liver, kidney, intestine

MDR1, multidrug resistance protein-1; MRP1, multidrug resistance-associated protein-1; NET, norepinephrine transporter; OATP, organic anionic transporter polypeptide; OCT, organic cationic transporter; SERT, serotonin reuptake transporter; VMAT, vesicular monoamine transporter.

**4. Endocytosis and exocytosis**

A few substances are so large or impermeant that they can enter cells only by endocytosis, the process by which the substance is bound at a cell-surface receptor, engulfed by the cell membrane, and carried into the cell by pinching off of the newly formed vesicle inside the membrane. The substance can then be released into the cytosol by breakdown of the vesicle membrane (see Figure 1-4D). This process is responsible for the transport of vitamin B<sub>12</sub>, complexed with a binding protein (intrinsic factor) across the wall of the gut into the blood. Similarly, iron is transported into hemoglobin-synthesizing red blood cell precursors in association with the protein transferrin. Specific receptors for the binding proteins must be present for this process to work.

The reverse process (exocytosis) is responsible for the secretion of many substances from cells. For example, many neurotransmitter substances are stored in membrane-bound vesicles in nerve endings to protect them from metabolic destruction in the cytoplasm. Appropriate activation of the nerve ending causes fusion of the storage vesicle with the cell membrane and expulsion of its contents into the extracellular space (see Chapter 6).

**B. Fick's Law of Diffusion**

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

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

where  $C_1$  is the higher concentration,  $C_2$  is the lower concentration, area is the cross-sectional area of the diffusion path, permeability coefficient is a measure of the mobility of the drug molecules in the medium of the diffusion path, and thickness is the length of the diffusion path. In the case of lipid diffusion, the lipid:aqueous partition coefficient is a major determinant of mobility of the drug because it determines how readily the drug enters the lipid membrane from the aqueous medium.

### C. Ionization of Weak Acids and Weak Bases; the Henderson-Hasselbalch Equation

The electrostatic charge of an ionized molecule attracts water dipoles and results in a polar, relatively water-soluble and lipid-insoluble complex. Because lipid diffusion depends on relatively high lipid solubility, ionization of drugs may markedly reduce their ability to permeate membranes. A very large percentage of the drugs in use are weak acids or weak bases; Table 1-4 lists some examples. For drugs, a weak acid is best defined as a neutral molecule that can reversibly dissociate into an anion (a negatively charged molecule) and a proton (a hydrogen ion). For example, aspirin dissociates as follows:

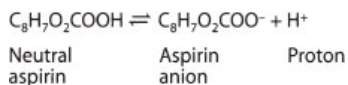


TABLE 1-4

#### Ionization constants of some common drugs.

Drug	pK <sub>a</sub> <sup>1</sup>
<b>Weak acids</b>	
Acetaminophen	9.5
Acetazolamide	7.2
Ampicillin	2.5
Aspirin	3.5
Atorvastatin	4.3
Chlorothiazide	6.8, 9.42
Chlorpropamide	5.0
Ciprofloxacin	6.1, 8.72
Cromolyn	2.0
Ethacrynic acid	2.5
Furosemide	3.9
Ibuprofen	4.4, 5.22
Levodopa	2.3
Methotrexate	4.8
Methyldopa	2.2, 9.22
Penicillamine	1.8

Pentobarbital	8.1
Phenobarbital	7.4
Phenytoin	8.3
Propylthiouracil	8.3
Salicylic acid	3.0
Sulfadiazine	6.5
Sulfapyridine	8.4
Theophylline	8.8
Tolbutamide	5.3
Warfarin	5.0
<b>Weak bases</b>	
Albuterol (salbutamol)	9.3
Allopurinol	9.4, 12.32
Alprenolol	9.6
Amiloride	8.7
Amiodarone	6.6
Amphetamine	9.8
Atropine	9.7
Bupivacaine	8.1
Chlordiazepoxide	4.6
Chloroquine	10.8, 8.4
Chlorpheniramine	9.2
Chlorpromazine	9.3
Clonidine	8.3
Cocaine	8.5
Codeine	8.2

Cyclizine	8.2
Desipramine	10.2
Diazepam	3.0
Diphenhydramine	8.8
Diphenoxylate	7.1
Ephedrine	9.6
Epinephrine	8.7
Ergotamine	6.3
Fluphenazine	8.0, 3.92
Hydralazine	7.1
Imipramine	9.5
Isoproterenol	8.6
Lidocaine	7.9
Metaraminol	8.6
Methadone	8.4
Methamphetamine	10.0
Methyldopa	10.6
Metoprolol	9.8
Morphine	7.9
Nicotine	7.9, 3.12
Norepinephrine	8.6
Pentazocine	7.9
Phenylephrine	9.8
Physostigmine	7.9, 1.82
Pilocarpine	6.9, 1.42
Pindolol	8.6

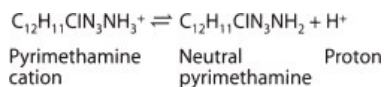
Procainamide	9.2
Procaine	9.0
Promethazine	9.1
Propranolol	9.4
Pseudoephedrine	9.8
Pyrimethamine	7.0–7.33
Quinidine	8.5, 4.42
Scopolamine	8.1
Strychnine	8.0, 2.32
Terbutaline	10.1
Thioridazine	9.5

<sup>1</sup>The  $pK_a$  is that pH at which the concentrations of the ionized and nonionized forms are equal.

<sup>2</sup>More than one ionizable group.

<sup>3</sup>Isoelectric point.

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



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

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

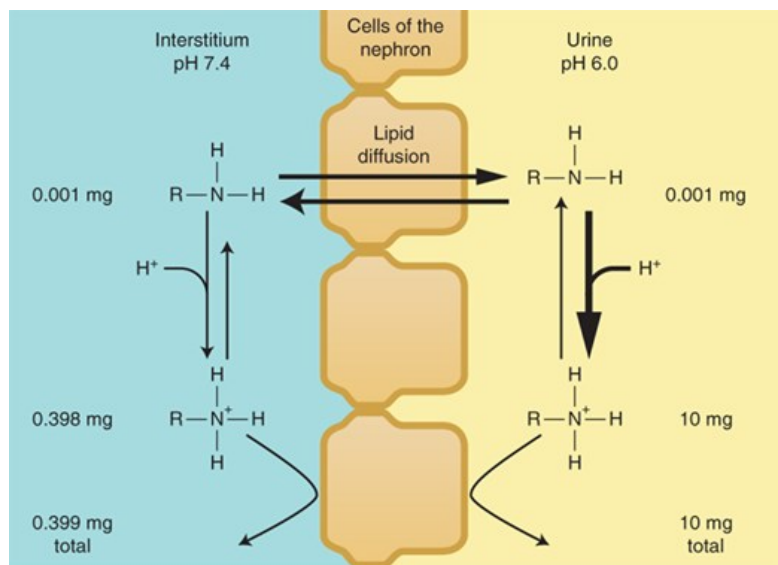
This equation applies to both acidic and basic drugs. Inspection confirms that the lower the pH relative to the  $pK_a$ , the greater will be the fraction of drug in the protonated form. Because the uncharged form is the more lipid-soluble, more of a weak acid will be in the lipid-soluble form at acid pH, whereas more of a basic drug will be in the lipid-soluble form at alkaline pH.

Application of this principle is made in the manipulation of drug excretion by the kidney (see [Case Study](#)). Almost all drugs are filtered at the glomerulus. If a drug is in a lipid-soluble form during its passage down the renal tubule, a significant fraction will be reabsorbed back into the tissue by simple passive diffusion. If the goal is to accelerate excretion of the drug (eg, in a case of drug overdose), it is important to prevent its reabsorption from the tubule. This can often be accomplished by adjusting urine pH to make certain that most of the drug is in the ionized state, as shown in [Figure 1–5](#). As a result of this partitioning effect, the drug is “trapped” in the urine. Thus, weak acids are usually excreted faster in alkaline urine; weak bases are usually excreted faster in acidic urine. Other body fluids in which pH differences from blood pH may cause trapping or reabsorption are the contents of the stomach (normal pH 1.9–3) and small intestine (pH 7.5–8), breast milk (pH 6.4–7.6), aqueous humor (pH 6.4–7.5), and vaginal and

prostatic secretions (pH 3.5–7).

FIGURE 1-5

Trapping of a weak base (methamphetamine) in the urine when the urine is more acidic than the blood. In the hypothetical case illustrated, the diffusible uncharged form of the drug has equilibrated across the membrane, but the total concentration (charged plus uncharged) in the urine (more than 10 mg) is 25 times higher than in the blood (0.4 mg).



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As indicated by Table 1-4, a large number of drugs are weak bases. Most of these bases are amine-containing molecules. The nitrogen of a neutral amine has three atoms associated with it plus a pair of unshared electrons (see the display that follows). The three atoms may consist of one carbon or a chain of carbon atoms (designated “R”) and two hydrogens (a **primary amine**), two carbons and one hydrogen (a **secondary amine**), or three carbon atoms (a **tertiary amine**). Each of these three forms may reversibly bind a proton with the unshared electrons. Some drugs have a fourth carbon-nitrogen bond; these are **quaternary amines**. However, the quaternary amine is permanently charged and has no unshared electrons with which to reversibly bind a proton. Therefore, primary, secondary, and tertiary amines may undergo reversible protonation and vary their lipid solubility with pH, but quaternary amines are always in the poorly lipid-soluble charged form.

Primary                  Secondary                  Tertiary                  Quaternary



## DRUG GROUPS

To learn each pertinent fact about each of the many hundreds of drugs mentioned in this book would be an impractical goal and, fortunately, is unnecessary. Almost all the several thousand drugs currently available can be arranged into about 70 groups. Many of the drugs within each group are very similar in pharmacodynamic actions and in their pharmacokinetic properties as well. For most groups, one or two **prototype drugs** can be identified that typify the most important characteristics of the group. This permits classification of other important drugs in the group as variants of the prototype, so that only the prototype must be learned in detail and, for the remaining drugs, only the differences from the prototype.

\*The capillaries of the brain, the testes, and some other tissues are characterized by the absence of pores that permit aqueous diffusion. They may also contain high concentrations of drug export pumps (MDR pump molecules; see text). These tissues are therefore protected or “sanctuary” sites from many circulating drugs.

# DRUG DEVELOPMENT & REGULATION

A truly new drug (one that does not simply mimic the structure and action of previously available drugs) requires the discovery of a new drug target, ie, the pathophysiologic process or substrate of a disease. Such discoveries are usually made in public sector institutions (universities and research institutes), and molecules that have beneficial effects on such targets are often discovered in the same laboratories. However, the development of new drugs usually takes place in industrial laboratories because optimization of a class of new drugs requires painstaking and expensive chemical, pharmacologic, and toxicologic research. In fact, much of the recent progress in the application of drugs to disease problems can be ascribed to the pharmaceutical industry including “big pharma,” the multibillion-dollar corporations that specialize in drug development and marketing. These companies are uniquely skilled in translating basic findings into successful therapeutic breakthroughs and profit-making “blockbusters” (see <https://clincalc.com/DrugStats/Top200Drugs.aspx>).

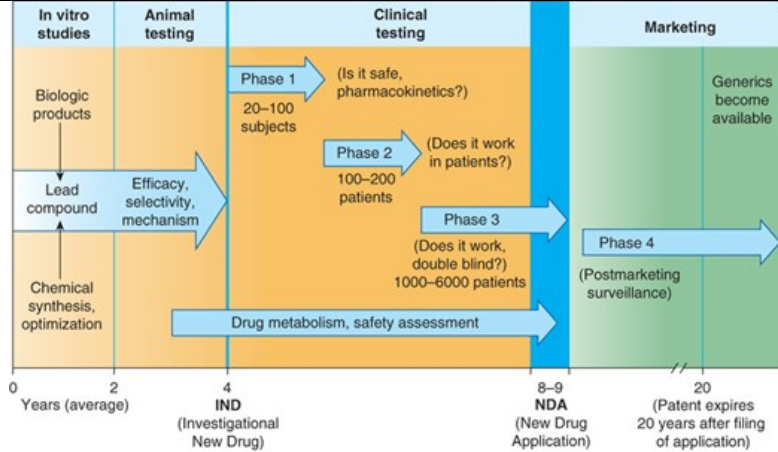
Such breakthroughs come at a price, however, and the escalating cost of drugs has become a significant contributor to the increase in the cost of health care. Development of new drugs is enormously expensive, but considerable controversy surrounds drug pricing. Drug prices in the United States have increased many-fold faster than overall price inflation. Critics claim that the costs of development and marketing drugs are grossly inflated by marketing activities, advertising, and other promotional efforts, which may consume as much as 25% or more of a company’s budget. Furthermore, profit margins for big pharma are relatively high. Recent drug-pricing scandals have been reported in which the rights to an older, established drug that requires no costly development have been purchased by a smaller company and the price increased by several hundred or several thousand percent. This “price gouging” has caused public outrage and attracted regulatory attention that may result in more legitimate and rational pricing mechanisms. Finally, pricing schedules for many drugs vary dramatically from country to country and even within countries, where large organizations can negotiate favorable prices and small ones cannot. Some countries have already addressed these inequities, and it seems likely that all countries will have to do so during the next few decades.

## NEW DRUG DEVELOPMENT

The development of a new drug usually begins with the discovery or synthesis of a potential new drug compound or the elucidation of a new drug target. After a new drug molecule is synthesized or extracted from a natural source, subsequent steps seek an understanding of the drug’s interactions with its biologic targets. Repeated application of this approach leads to synthesis of related compounds with increased efficacy, potency, and selectivity (Figure 1–6). In the United States, the safety and efficacy of drugs must be established before marketing can be legally carried out. In addition to in vitro studies, relevant biologic effects, drug metabolism, pharmacokinetic profiles, and relative safety of the drug are recommended to be characterized in vivo in animals before human drug trials can be started but not necessary if studies can be carried out in cells or alternative approaches. With regulatory approval, human testing may then go forward (usually in three phases) before the drug is considered for approval for general use. A fourth phase of data gathering and safety monitoring is becoming increasingly important and follows after approval for marketing. Once approved, the great majority of drugs become available for use by any appropriately licensed practitioner. Highly toxic drugs that are nevertheless considered valuable in lethal diseases may be approved for restricted use by practitioners who have undergone special training in their use and who maintain detailed records.

### FIGURE 1–6

The development and testing process required to bring a drug to market in the USA. Some of the requirements may be different for drugs used in life-threatening diseases (see text).



Source: Todd W. Vanderah:  
Basic & Clinical Pharmacology, Sixteenth Edition  
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## DRUG DISCOVERY

Most new drugs or drug products are discovered or developed through the following approaches: (1) screening for biologic activity of large numbers of natural products, banks of previously discovered chemical entities, or large libraries of peptides, nucleic acids, and other organic molecules; (2) chemical modification of a known active molecule, resulting in a “me-too” analog; (3) identification or elucidation of a new drug target, which suggests molecules that will hit that target; and (4) rational design of a new molecule based on an understanding of biologic mechanisms and drug receptor structure. Steps (3) and (4) are often carried out in academic research laboratories and are more likely to lead to breakthrough drugs, but the costs of steps (1) and (2) usually ensure that industry carries them out.

Once a new drug target or promising molecule has been identified, the process of moving from the basic science laboratory to the clinic begins. This **translational research** involves the preclinical and clinical steps described next. While clinical trials in humans are required only for drugs to be used in humans, all of the other steps described apply to veterinary drugs as well as drugs for human diseases.

## Drug Screening

Drug screening involves a variety of assays at the molecular, cellular, organ system, and whole animal levels to define the **pharmacologic profile**, ie, the activity and selectivity of the drug. The type and number of initial screening tests depend on the pharmacologic and therapeutic goal. For example, anti-infective drugs are tested against a variety of infectious organisms, some of which are resistant to standard agents; hypoglycemic drugs are tested for their ability to lower blood sugar, etc.

The candidate molecule is also studied for a broad array of other actions to determine the mechanism of action and selectivity of the drug. This can reveal both expected and unexpected toxic effects. Occasionally, an unexpected therapeutic action is serendipitously discovered by a careful observer; for example, the era of modern diuretics was initiated by the observation that certain antimicrobial sulfonamides caused metabolic acidosis in patients. The selection of compounds for development is most efficiently conducted in animal models of human disease. Where good predictive preclinical models exist (eg, infection, hypertension, or thrombotic disease), we generally have good or excellent drugs. Good drugs or breakthrough improvements are conspicuously lacking and slow for diseases for which preclinical models are poor or not yet available, eg, autism and Alzheimer disease.

At the molecular level, the candidate compound would be screened for activity on the target, for example, receptor binding affinity to cell membranes containing the homologous animal receptors (or if possible, on the cloned human receptors). Early studies would be done to predict effects that might later cause undesired drug metabolism or toxicologic complications. For example, studies on liver cytochrome P450 enzymes would be performed to determine whether the molecule of interest is likely to be a substrate or inhibitor of these enzymes or to alter the metabolism of other drugs.

Effects on cell function determine whether the drug is an agonist, partial agonist, inverse agonist, or antagonist at relevant receptors. Isolated tissues would be used to characterize the pharmacologic activity and selectivity of the new compound in comparison with reference compounds. Comparison with other drugs would also be undertaken in a variety of in vivo studies. At each step in this process, the compound would have to meet specific

performance and selectivity criteria to be carried further.

Whole animal studies are generally necessary to determine the effect of the drug on organ systems and disease models. Cardiovascular and renal function studies of new drugs are generally first performed in normal animals. Studies on disease models, if available, are then performed. For a candidate antihypertensive drug, animals with hypertension would be treated to see whether blood pressure was lowered in a dose-related manner and to characterize other effects of the compound. Evidence would be collected on duration of action and efficacy after oral and parenteral administration. If the agent possessed useful activity, it would be further studied for possible adverse effects on other organs, including the respiratory, gastrointestinal, renal, endocrine, and central nervous systems.

These studies might suggest the need for further chemical modification (compound optimization) to achieve more desirable pharmacokinetic or pharmacodynamic properties. For example, oral administration studies might show that the drug was poorly absorbed or rapidly metabolized in the liver; modification to improve bioavailability might be indicated. If the drug is to be administered long term, an assessment of tolerance development would be made. For drugs related to or having mechanisms of action similar to those known to cause physical or psychological dependence in humans, ability to cause dependence in animals would also be studied. Drug interactions would be examined.

The desired result of this screening procedure (which may have to be repeated several times with congeners of the original molecule) is a **lead compound**, ie, a leading candidate for a successful new drug. A patent application would be filed for a novel compound (a *composition of matter* patent) that is efficacious, or for a new and nonobvious therapeutic use (a *use patent*) for a previously known chemical entity.

## PRECLINICAL SAFETY & TOXICITY TESTING

*All chemicals are toxic in some individuals at some dose.* Candidate drugs that survive the initial screening procedures must be carefully evaluated for potential risks before and during clinical testing. Depending on the proposed use of the drug, preclinical toxicity testing includes most or all of the procedures shown in [Table 1-5](#). Although no chemical can be certified as completely “safe” (free of risk), the objective is to estimate the risk associated with exposure to the drug candidate and to consider this in the context of therapeutic needs and likely duration of drug use.

TABLE 1-5

### Safety tests.

Type of Test	Approach and Goals
Acute toxicity	Usually two species, two routes. Determine the no-effect dose and the maximum tolerated dose. In some cases, determine the acute dose that is lethal in approximately 50% of animals.
Subacute or subchronic toxicity	Three doses, two species. Two weeks to 3 months of testing may be required before clinical trials. The longer the duration of expected clinical use, the longer the subacute test. Determine biochemical, physiologic effects.
Chronic toxicity	Rodent and at least one nonrodent species for $\geq 6$ months. Required when drug is intended to be used in humans for prolonged periods. Usually run concurrently with clinical trials. Determine same end points as subacute toxicity tests.
Effect on reproductive performance	Two species, usually one rodent and rabbits. Test effects on animal mating behavior, reproduction, parturition, progeny, birth defects, postnatal development.
Carcinogenic potential	Two years, two species. Required when drug is intended to be used in humans for prolonged periods. Determine gross and histologic pathology.
Mutagenic potential	Test effects on genetic stability and mutations in bacteria (Ames test) or mammalian cells in culture; dominant lethal test and clastogenicity in mice.

The goals of preclinical toxicity studies include identifying potential human toxicities, designing tests to further define the toxic mechanisms, and predicting the most relevant toxicities to be monitored in clinical trials. In addition to the studies shown in [Table 1–5](#), several quantitative estimates are desirable. These include the **no-effect dose**—the maximum dose at which a specified toxic effect is not seen; the **minimum lethal dose**—the smallest dose that is observed to kill any experimental animal; and, if necessary, the **median lethal dose (LD<sub>50</sub>)**—the dose that kills approximately 50% of the animals in a test group. Presently, the LD<sub>50</sub> is estimated from the smallest number of animals possible. These doses are used to calculate the initial dose to be tried in humans, usually taken as one hundredth to one tenth of the no-effect dose in animals.

It is important to recognize the limitations of preclinical testing. These include the following:

1. Toxicity testing is time-consuming and expensive. Two to 6 years may be required to collect and analyze data on toxicity before the drug can be considered ready for testing in humans.
2. Large numbers of animals may be needed to obtain valid preclinical data. Scientists are properly concerned about this situation, and progress has been made toward reducing the numbers required while still obtaining valid data. Cell and tissue culture in vitro methods and computer modeling are increasingly being used, but their predictive value is still limited. Nevertheless, some segments of the public attempt to halt all animal testing in the unfounded belief that it has become unnecessary.
3. Extrapolations of toxicity data from animals to humans are reasonably predictive for many but not for all toxicities.
4. For statistical reasons, rare adverse effects are unlikely to be detected in preclinical testing.

## EVALUATION IN HUMANS

A very small fraction of lead compounds reach clinical trials, and less than one-third of the drugs studied in humans survive clinical trials and reach the marketplace. Federal law in the USA and ethical considerations require that the study of new drugs in humans be conducted in accordance with stringent guidelines. Scientifically valid results are not guaranteed simply by conforming to government regulations, however, and the design and execution of a good clinical trial require interdisciplinary personnel including basic scientists, clinical pharmacologists, clinician specialists, statisticians, and others. The current standard for clinical trials is known as the randomized controlled trial (RCT) and is described below. The need for careful design and execution is based on three major confounding factors inherent in the study of any drug in humans.

### Confounding Factors in Clinical Trials

#### A. The Variable Natural History of Most Diseases

Many diseases tend to wax and wane in severity; some disappear spontaneously, even, on occasion, cancer. A good experimental design takes into account the natural history of the disease by evaluating a large enough population of subjects over a sufficient period of time. Further protection against errors of interpretation caused by disease fluctuations is sometimes provided by using a **crossover design**, which consists of alternating periods of administration of test drug, placebo preparation (the control), and the previous standard treatment (positive control), if any, in each subject. These sequences are systematically varied so that different subsets of patients receive each of the possible sequences of treatment.

#### B. The Presence of Other Diseases and Risk Factors

Known and unknown diseases and risk factors (including lifestyles of subjects) may influence the results of a clinical study. For example, some diseases alter the pharmacokinetics of drugs (see [Chapters 3 through 5](#)). Other drugs and some foods alter the pharmacokinetics of many drugs. Concentrations of blood or tissue components being monitored as a measure of the effect of the new agent may be influenced by other diseases or other drugs. Attempts to avoid this hazard usually involve the crossover technique (when feasible) and proper selection and assignment of patients to each of the study groups. This requires obtaining accurate diagnostic tests and medical and pharmacologic histories (including use of recreational drugs, over-the-counter drugs, and “supplements”) and the use of statistically valid methods of randomization in assigning subjects to particular study groups. There is growing interest in analyzing genetic variations as part of the trial that may influence whether a person responds to a particular drug. It has been shown that age, gender, and pregnancy influence the pharmacokinetics of some drugs, but these factors have not been adequately studied because of legal restrictions and reluctance to expose these populations to unknown risks.

### C. Subject and Observer Bias and Other Factors

Most patients tend to respond in a positive way to any therapeutic intervention by interested, caring, and enthusiastic medical personnel. The manifestation of this phenomenon in the subject is the **placebo response** (Latin, “I shall please”) and may involve objective physiologic and biochemical changes as well as changes in subjective complaints associated with the disease. The placebo response is usually quantitated by administration of an inert material with exactly the same physical appearance, odor, consistency, etc, as the active dosage form. The magnitude of the response varies considerably from patient to patient and may also be influenced by the duration of the study. In some conditions, a positive response may be noted in as many as 30–40% of subjects given placebo. Placebo adverse effects and “toxicity” also occur but usually involve subjective effects: stomach upset, insomnia, sedation, and so on.

Subject bias effects can be quantitated—and minimized relative to the response measured during active therapy—by the **single-blind** design. This involves use of a placebo as described above, administered to the same subjects in a crossover design, if possible, or to a separate control group of well-matched subjects. Observer bias can be taken into account by disguising the identity of the medication being used—placebo or active form—from both the subjects and the personnel evaluating the subjects’ responses (**double-blind** design). In this design, a third party holds the code identifying each medication packet, and the code is not broken until all the clinical data have been collected.

Drug effects seen in clinical trials are obviously affected by the patient taking the drugs at the dose and frequency prescribed. In a recent phase 2 study, one-third of the patients who said they were taking the drug were found by blood analysis to have not taken the drug. Confirmation of **compliance** with protocols (also known as **adherence**) is a necessary element to consider.

The various types of studies and the conclusions that may be drawn from them are described in the accompanying text box. (See Box: [Drug Studies—The Types of Evidence.](#))

## Drug Studies—The Types of Evidence\*

As described in this chapter, drugs are studied in a variety of ways, from 30-minute test tube experiments with isolated enzymes and receptors to decades-long observations of populations of patients. The conclusions that can be drawn from such different types of studies can be summarized as follows.

*Basic research* is designed to answer specific, usually single, questions under tightly controlled laboratory conditions, eg, does drug *x* inhibit enzyme *y*? The basic question may then be extended, eg, if drug *x* inhibits enzyme *y*, what is the concentration-response relationship? Such experiments are usually reproducible and often lead to reliable insights into the mechanism of the drug's action.

*First-in-human* studies include phase 1–3 trials. Once a drug receives FDA approval for use in humans, *case reports* and *case series* consist of observations by clinicians of the effects of drug (or other) treatments in one or more patients. These results often reveal unpredictable benefits and toxicities but do not generally test a prespecified hypothesis and cannot prove cause and effect. *Analytic* epidemiologic studies consist of observations designed to test a specified hypothesis, eg, that thiazolidinedione antidiabetic drugs are associated with adverse cardiovascular events. *Cohort* epidemiologic studies utilize populations of patients that have (exposed group) and have not (control group) been exposed to the agents under study and ask whether the exposed groups show a higher or lower incidence of the effect. *Case-control* epidemiologic studies utilize populations of patients that have displayed the end point under study and ask whether they have been exposed or not exposed to the drugs in question. Such epidemiologic studies add weight to conjectures but cannot control all confounding variables and therefore cannot conclusively prove cause and effect.

*Meta-analyses* utilize rigorous evaluation and grouping of similar studies to increase the number of subjects studied and hence the statistical power of results obtained in multiple published studies. While the numbers may be dramatically increased by meta-analysis, the individual studies still suffer from their varying methods and end points, and a meta-analysis cannot prove cause and effect.

*Large randomized controlled trials (RCTs)* are designed to answer specific questions about the effects of medications on clinical end points or important surrogate end points, using large enough samples of patients and allocating them to control and experimental treatments using rigorous randomization methods. Randomization is the best method for distributing all foreseen confounding factors, as well as unknown confounders, equally between the experimental and control groups. When properly carried out, such studies are rarely invalidated and are considered the gold standard in evaluating drugs.

A critical factor in evaluating the data regarding a new drug is *access to all the data*. Unfortunately, many large studies are never published because the results are negative, ie, the new drug is *not* better than the standard therapy. This *missing data* phenomenon falsely exaggerates the benefits of new drugs because negative results are hidden.

\*We thank Ralph Gonzales, MD, for helpful comments.

## The Food & Drug Administration

The FDA is the administrative body that oversees the drug evaluation process in the USA and grants approval for marketing of new drug products. To receive FDA approval for marketing, the originating institution or company (almost always the latter) must submit evidence of safety and effectiveness. Outside the USA, the regulatory and drug approval process is generally similar to that in the USA.

As its name suggests, the FDA is also responsible for certain aspects of food safety, a role it shares with the US Department of Agriculture (USDA). Shared responsibility results in complications when questions arise regarding the use of drugs, eg, antibiotics, in food animals. A different type of problem arises when so-called food supplements are found to contain active drugs, eg, [sildenafil](#) analogs in “energy food” supplements.

The FDA's authority to regulate drugs derives from specific legislation ([Table 1–6](#)). If a drug has not been shown through adequately controlled testing to be “safe and effective” for a specific use, it cannot be marketed in interstate commerce for this use.\*

TABLE 1–6

### Some major legislation pertaining to drugs in the USA.

Law	Purpose and Effect
Pure Food and Drug Act of 1906	Prohibited mislabeling and adulteration of drugs.
Opium Exclusion Act of 1909	Prohibited importation of opium.
Amendment (1912) to the Pure Food and Drug Act	Prohibited false or fraudulent advertising claims.
Harrison Narcotic Act of 1914	Established regulations for use of opium, opiates, and <a href="#">cocaine</a> (marijuana added in 1937).
Food, Drug, and Cosmetic Act of 1938	Required that new drugs be safe as well as pure (but did not require proof of efficacy). Enforcement by the FDA.
Durham-Humphrey Act of 1952	Vested in the FDA the power to determine which products could be sold without prescription.
Kefauver-Harris Amendments (1962) to the Food, Drug, and Cosmetic Act	Required proof of efficacy as well as safety for new drugs and for drugs released since 1938; established guidelines for reporting of information about adverse reactions, clinical testing, and advertising of new drugs.
Comprehensive Drug Abuse Prevention and Control Act (1970)	Outlined strict controls in the manufacture, distribution, and prescribing of habit-forming drugs; established drug schedules and programs to prevent and treat drug addiction.
Orphan Drug Amendment of 1983	Provided incentives for development of drugs that treat diseases with fewer than 200,000 patients in the USA.
Drug Price Competition and Patent Restoration Act of 1984	Abbreviated new drug applications for generic drugs. Required bioequivalence data. Patent life extended by amount of time drug delayed by FDA review process. Cannot exceed 5 extra years or extend to more than 14 years post-NDA approval.
Prescription Drug User Fee Act (1992, reauthorized 2007, 2012)	Manufacturers pay user fees for certain new drug applications. "Breakthrough" products may receive special category approval after expanded phase 1 trials (2012).
Dietary Supplement Health and Education Act (1994)	Established standards with respect to dietary supplements but prohibited full FDA review of supplements and botanicals as drugs. Required the establishment of specific ingredient and nutrition information labeling that defines dietary supplements and classifies them as part of the food supply but allows unregulated advertising.
Bioterrorism Act of 2002	Enhanced controls on dangerous biologic agents and toxins. Seeks to protect safety of food, water, and drug supply.
Food and Drug Administration Amendments Act of 2007	Granted the FDA greater authority over drug marketing, labeling, and direct-to-consumer advertising; required post-approval studies, established active surveillance systems, made clinical trial operations and results more visible to the public.

Biologics Price Competition and Innovation Act of 2009	Authorized the FDA to establish a program of abbreviated pathways for approval of “biosimilar” biologics (generic versions of monoclonal antibodies, etc).
FDA Safety and Innovation Act of 2012	Renewed FDA authorization for accelerated approval of urgently needed drugs; established new accelerated process, “breakthrough therapy,” in addition to “priority review,” “accelerated approval,” and “fast-track” procedures.
Drug Quality and Security Act of 2013	Granted the FDA more authority to regulate and monitor the manufacturing of compounded drugs.

Unfortunately, “safe” can mean different things to the patient, the physician, and society. Complete absence of risk is impossible to demonstrate, but this fact may not be understood by members of the public, who frequently assume that any medication sold with the approval of the FDA should be free of serious “side effects.” This confusion is a major factor in litigation and dissatisfaction with aspects of drugs and medical care.

The history of drug regulation in the USA (see [Table 1–6](#)) reflects several health events that precipitated major shifts in public opinion. For example, the Federal Food, Drug, and Cosmetic Act of 1938 was largely a reaction to deaths associated with the use of a preparation of [sulfanilamide](#) marketed before it and its vehicle were adequately tested. Similarly, the Kefauver-Harris Amendments of 1962 were, in part, the result of a teratogenic drug disaster involving [thalidomide](#). This agent was introduced in Europe in 1957–1958 and was marketed as a “nontoxic” hypnotic and promoted as being especially useful as a sleep aid during pregnancy. In 1961, reports were published suggesting that [thalidomide](#) was responsible for a dramatic increase in the incidence of a rare birth defect called phocomelia, a condition involving shortening or complete absence of the arms and legs. Epidemiologic studies provided strong evidence for the association of this defect with [thalidomide](#) use by women during the first trimester of pregnancy, and the drug was withdrawn from sale worldwide. An estimated 10,000 children were born with birth defects because of maternal exposure to this one agent. The tragedy led to the requirement for more extensive testing of new drugs for teratogenic effects and stimulated passage of the Kefauver-Harris Amendments of 1962, even though the drug was not then approved for use in the USA. Despite its disastrous fetal toxicity and effects in pregnancy, [thalidomide](#) is a relatively safe drug for humans other than the fetus. Even the most serious risk of toxicities may be avoided or managed if understood, and despite its toxicity, [thalidomide](#) is now approved by the FDA for limited use as a potent immunoregulatory agent and to treat certain forms of leprosy.

### Clinical Trials: The IND & NDA

Once a new drug is judged ready to be studied in humans, a Notice of Claimed Investigational Exemption for a New Drug (IND) must be filed with the FDA (see [Figure 1–6](#)). The IND includes (1) information on the composition and source of the drug, (2) chemical and manufacturing information, (3) all data from animal studies, (4) proposed plans for clinical trials, (5) the names and credentials of physicians who will conduct the clinical trials, and (6) a compilation of the key preclinical data relevant to study of the drug in humans that have been made available to investigators and their institutional review boards.

It often requires 4–6 years of clinical testing to accumulate and analyze all required data. Testing in humans is begun only after sufficient acute and subacute animal toxicity studies have been completed. Chronic safety testing in animals, including carcinogenicity studies, is usually done concurrently with clinical trials. In each phase of the clinical trials, volunteers or patients must be informed of the investigational status of the drug as well as the possible risks and must be allowed to decline or to consent to participate and receive the drug. In addition to the approval of the sponsoring organization and the FDA, an interdisciplinary institutional review board (IRB) at each facility where the clinical drug trial will be conducted must review and approve the scientific and ethical plans for testing in humans.

In **phase 1**, the effects of the drug as a function of dosage are established in a small number (20–100) of healthy volunteers. If the drug is expected to have significant toxicity, as may be the case in cancer and AIDS therapy, volunteer patients with the disease participate in phase 1 rather than normal volunteers. Phase 1 trials are done to determine the probable limits of the safe clinical dosage range. These trials may be nonblind or “open”; that is, both the investigators and the subjects know what is being given. Alternatively, they may be “blinded” and placebo controlled. Many predictable toxicities are detected in this phase. Pharmacokinetic measurements of absorption, half-life, and metabolism are often done. Phase 1 studies are usually performed in research centers by specially trained clinical pharmacologists.

In **phase 2**, the drug is studied in patients with the target disease to determine its efficacy (“proof of concept” studies), and the doses to be used in any follow-on trials. A modest number of patients (100–200) are studied in detail. A single-blind design may be used, with an inert placebo medication and an established active drug (positive control) in addition to the investigational agent. Phase 2 trials are usually done in special clinical centers (eg, university hospitals). A broader range of toxicities may be detected in this phase. Phase 2 trials have the highest rate of drug failures, and only 25% of innovative drugs move on to phase 3.

In **phase 3**, the drug is evaluated in much larger numbers—usually thousands—of patients with the target disease to further establish and confirm safety and efficacy. Using information gathered in phases 1 and 2, phase 3 trials are designed to minimize errors caused by placebo effects, variable course of the disease, etc. Therefore, double-blind and crossover techniques are often used. Phase 3 trials are usually performed in settings similar to those anticipated for the ultimate use of the drug. Phase 3 studies can be difficult to design and execute and are usually expensive because of the large numbers of patients involved and the masses of data that must be collected and analyzed. The drug is formulated as intended for the market. The investigators are usually specialists in the disease being treated. Certain toxic effects, especially those caused by immunologic processes, may first become apparent in phase 3.

If phase 3 results meet expectations, application is made for permission to market the new agent. Marketing approval requires submission of a New Drug Application (NDA)—or for biologicals, a Biological License Application (BLA)—to the FDA. The application contains, often in hundreds of volumes, full reports of all preclinical and clinical data pertaining to the drug under review. The number of subjects studied in support of new drug applications has been increasing and currently averages more than 5000 patients for new drugs of novel structure (new molecular entities). The duration of the FDA review leading to approval (or denial) of the new drug application may vary from months to years. If problems arise, eg, unexpected but possibly serious toxicities, additional studies may be required and the review process may extend to several additional years.

Many phase 2 and phase 3 studies attempt to measure a new drug’s “noninferiority” to the placebo or a standard treatment. Interpretation of the results may be difficult because of unexpected confounding variables, loss of subjects from some groups, or realization that results differ markedly between certain subgroups within the active treatment (new drug) group. Older statistical methods for evaluating drug trials often fail to provide definitive answers when these problems arise. Therefore, new “adaptive” statistical methods are under development that allow changes in the study design when interim data evaluation indicates the need. Preliminary results with such methods suggest that they may allow decisions regarding superiority as well as noninferiority, shortening of trial duration, discovery of new therapeutic benefits, and more reliable conclusions regarding the results (see Bhatt & Mehta, 2016).

In cases of urgent need (eg, cancer chemotherapy), the process of preclinical and clinical testing and FDA review may be accelerated. For serious diseases, the FDA may permit extensive but controlled marketing of a new drug before phase 3 studies are completed; for life-threatening diseases, it may permit controlled marketing even before phase 2 studies have been completed. “Fast track,” “priority approval,” and “accelerated approval” are FDA programs that are intended to speed entry of new drugs into the marketplace. In 2012, an additional special category of “breakthrough” products (eg, for cystic fibrosis) was approved for restricted marketing after expanded phase 1 trials (see [Table 1–6](#)). Roughly 50% of drugs in phase 3 trials enter early, controlled marketing. Such accelerated approval is usually granted with the requirement that careful monitoring of the effectiveness and toxicity of the drug be carried out and reported to the FDA. Unfortunately, FDA enforcement of this requirement has not always been adequate.

Once approval to market a drug has been obtained, **phase 4** begins. This constitutes monitoring the safety of the new drug under actual conditions of use in large numbers of patients. The importance of careful and complete reporting of toxicity by physicians after marketing begins can be appreciated by noting that many important drug-induced effects have an incidence of 1 in 10,000 or less and that some adverse effects may become apparent only after chronic dosing. The sample size required to disclose drug-induced events or toxicities is very large for such rare events. For example, several hundred thousand patients may have to be exposed before the first case is observed of a toxicity that occurs with an average incidence of 1 in 10,000. Therefore, low-incidence drug effects are not generally detected before phase 4 no matter how carefully phase 1, 2, and 3 studies are executed. Phase 4 has no fixed duration. As with monitoring of drugs granted accelerated approval, phase 4 monitoring has often been lax.

The time from the filing of a patent application (which usually precedes clinical trials) to approval for marketing of a new drug may be 5 years or considerably longer. Since the lifetime of a patent is 20 years in the USA, the owner of the patent (usually a pharmaceutical company) has exclusive rights for marketing the product for only a limited time after approval of the new drug application. Because the FDA review process itself can be lengthy (300–500 days for evaluation of an NDA), the time consumed by the review is sometimes added to the patent life. However, the extension (up to 5 years) cannot increase the total life of the patent to more than 14 years after approval of a new drug application. The Patient Protection and Affordable Care Act of 2010 provides for 12 years of patent protection for new drugs. After expiration of the patent, any company may produce the drug, file an

abbreviated new drug application (ANDA), demonstrate equivalence, and, with FDA approval, market the drug as a **generic** product without paying license fees to the original patent owner. Currently, more than half of prescriptions in the USA are for generic drugs. Even biotechnology-based drugs such as antibodies and other proteins are now qualifying for generic (“biosimilar”) designation, and this has fueled regulatory concerns. More information on drug patents is available at the FDA website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm>.

A **trademark** is a drug’s proprietary trade name and is usually registered; this registered name may be legally protected as long as it is used. A generically equivalent product, unless specially licensed, cannot be sold under the trademark name and is often designated by the official generic name. Generic prescribing is described in [Chapter 66](#).

### Conflicts of Interest

Several factors in the development and marketing of drugs result in conflicts of interest. Use of pharmaceutical industry funding to support FDA approval processes raises the possibility of conflicts of interest within the FDA. Supporters of this practice point out that chronic FDA underfunding by the government allows for few alternatives. Another important source of conflicts of interest is the dependence of the FDA on outside panels of experts who are recruited from the scientific and clinical community to advise the government agency on questions regarding drug approval or withdrawal. Such experts are often recipients of grants from the companies producing the drugs in question. The need for favorable data in the new drug application leads to phase 2 and 3 trials in which the new agent is compared only to placebo, not to older, effective drugs. As a result, data regarding the efficacy and toxicity of the new drug *relative to a known effective agent* may not be available when the new drug is first marketed.

Manufacturers promoting a new agent may pay physicians to use it in preference to older drugs with which they are more familiar. Manufacturers sponsor small and often poorly designed clinical studies after marketing approval and aid in the publication of favorable results but may retard publication of unfavorable results. The need for physicians to meet continuing medical education (CME) requirements in order to maintain their licenses encourages manufacturers to sponsor conferences and courses, often in highly attractive vacation sites, and new drugs are often featured in such courses. The common practice of distributing free samples of new drugs to practicing physicians has both positive and negative effects. The samples allow physicians to try out new drugs without incurring any cost to the patient. On the other hand, new drugs are usually much more expensive than older agents, and when the free samples run out, the patient (or insurance carrier) may be forced to pay much more for treatment than if the older, cheaper, and possibly equally effective drug were used. Finally, when the patent for a drug is nearing expiration, the patent-holding manufacturer may try to extend its exclusive marketing status by paying generic manufacturers to *not* introduce a generic version (“pay to delay”).

### Adverse Drug Reactions

An adverse drug event (ADE) or reaction to a drug (ADR) is a harmful or unintended response. Adverse drug reactions are claimed to be the fourth leading cause of death, higher than pulmonary disease, AIDS, accidents, and automobile deaths. The FDA has further estimated that 300,000 preventable adverse events occur annually in hospitals, many as a result of confusing medical information or lack of information (eg, regarding drug incompatibilities). Adverse reactions occurring only in certain susceptible patients include intolerance, idiosyncrasy (frequently genetic in origin), and allergy (usually immunologically mediated). During IND studies and clinical trials before FDA approval, all adverse events (serious, life-threatening, disabling, reasonably drug related, or unexpected) must be reported. After FDA approval to market a drug, surveillance, evaluation, and reporting must continue for any adverse events that are related to use of the drug, including overdose, accident, failure of expected action, events occurring from drug withdrawal, and unexpected events not listed in labeling. Events that are both serious and unexpected must be reported to the FDA within 15 days. The ability to predict and avoid adverse drug reactions and optimize a drug’s therapeutic index is an increasing focus of pharmacogenetic and personalized (also called “precision”) medicine. It has been suggested that greater use of electronic health records will reduce some of these risks (see [Chapter 66](#)). This hope has not yet been realized.

### Orphan Drugs & Treatment of Rare Diseases

Drugs for rare diseases—so-called orphan drugs—can be difficult to research, develop, and market. Proof of drug safety and efficacy in small populations must be established, but doing so is a complex process. Furthermore, because basic research in the pathophysiology and mechanisms of rare diseases receives relatively little attention or funding in both academic and industrial settings, recognized rational targets for drug action may be few. In addition, the cost of developing a drug can greatly influence priorities when the target population is relatively small. Funding for development of drugs for rare diseases or ignored diseases that do not receive priority attention from the traditional industry has received increasing support via philanthropy or similar funding from not-for-profit foundations such as the Cystic Fibrosis Foundation, the Michael J. Fox Foundation for Parkinson’s

The Orphan Drug Amendment of 1983 provides incentives for the development of drugs for treatment of a rare disease or condition defined as “any disease or condition which (a) affects less than 200,000 persons in the USA or (b) affects more than 200,000 persons in the USA but for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug.” Since 1983, the FDA has approved for marketing more than 300 orphan drugs to treat more than 82 rare diseases.

\*Although the FDA does not directly control drug commerce within states, a variety of state and federal laws control interstate production and marketing of drugs.

## SOURCES OF INFORMATION

Students who wish to review the field of pharmacology in preparation for an examination are referred to *Pharmacology: Examination and Board Review*, by Katzung, Kruidering-Hall, Lalchandani Tuan, Vanderah, and Trevor (McGraw Hill, 2021). This book provides approximately 1000 questions and explanations in USMLE format. A short study guide is *USMLE Road Map: Pharmacology*, by Katzung and Trevor (McGraw Hill, 2006). *Road Map* contains numerous tables, figures, mnemonics, and USMLE-type clinical vignettes.

The references at the end of each chapter in this book were selected to provide reviews or classic publications of information specific to those chapters. More detailed questions relating to basic or clinical research are best answered by referring to the journals covering general pharmacology and clinical specialties. For the student and the physician, three periodicals can be recommended as especially useful sources of current information about drugs: *The New England Journal of Medicine*, which publishes much original drug-related clinical research as well as frequent reviews of topics in pharmacology; *The Medical Letter on Drugs and Therapeutics*, which publishes brief critical reviews of new and old therapies; and *Prescriber's Letter*, a monthly comparison of new and older drug therapies with much useful advice. On the Internet/World Wide Web, two sources can be particularly recommended: the Cochrane Collaboration and the FDA site (see reference list below).

Other sources of information pertinent to the United States should be mentioned as well. The “package insert” is a summary of information that the manufacturer is required to place in the prescription sales package; *Physicians' Desk Reference (PDR)* is a compendium of package inserts published annually with supplements twice a year. It is sold in bookstores and distributed to licensed physicians. The package insert consists of a brief description of the pharmacology of the product. This brochure contains much practical information, but also lists every toxic effect ever reported, no matter how rare, thus shifting responsibility for adverse drug reactions from the manufacturer to the prescriber. A black box warning, if included, is of medicolegal importance, because it indicates a potentially lethal adverse effect. *UpToDate.com* is a large subscription website containing detailed descriptions of current standards of care, including drug therapy, for a wide variety of clinical conditions. *Micromedex* and *Lexi-Comp* are extensive subscription websites. They provide downloads for personal digital assistant devices, online drug dosage and interaction information, and toxicologic information. A useful and objective quarterly handbook that presents information on drug toxicity and interactions is *Drug Interactions: Analysis and Management*. Finally, the FDA maintains an Internet website that carries news regarding recent drug approvals, withdrawals, warnings, etc. It can be accessed at <http://www.fda.gov>. The MedWatch drug safety program is a free e-mail notification service that provides news of FDA drug warnings and withdrawals. Subscriptions may be obtained at <https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program>.

### CASE STUDY ANSWER

**Aspirin** overdose commonly causes a mixed respiratory alkalosis and metabolic acidosis. Because **aspirin** is a weak acid, serum acidosis favors entry of the drug into tissues (increasing toxicity), and urinary acidosis favors reabsorption of excreted drug back into the blood (prolonging the effects of the overdose). Sodium bicarbonate, a weak base, is an important component of the management of **aspirin** overdose. It causes alkalosis, reducing entry into tissues, and increases the pH of the urine, enhancing renal clearance of the drug. See the discussion of the ionization of weak acids and weak bases in the text.

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## Chapter 2: Drug Receptors & Pharmacodynamics

Mark von Zastrow

### CASE STUDY

#### CASE STUDY

A 51-year-old man presents to the emergency department due to acute difficulty breathing. The patient is afebrile and normotensive but anxious, tachycardic, and markedly tachypneic. Auscultation of the chest reveals diffuse wheezes. The clinician provisionally makes the diagnosis of bronchial asthma and administers **epinephrine** by intramuscular injection, improving the patient's breathing over several minutes. A normal chest x-ray and electrocardiogram are subsequently obtained, and the medical history is remarkable only for mild hypertension that is being treated with **propranolol**. The clinician instructs the patient to discontinue use of **propranolol** and changes the patient's antihypertensive medication to **verapamil**. Why is the clinician correct to discontinue **propranolol**? Why is **verapamil** likely to be a more suitable choice for managing hypertension in this patient? Are there alternative pharmacotherapies that the clinician should also consider?

Therapeutic and toxic effects of drugs result from their interactions with molecules in the patient. Most drugs act by associating with specific macromolecules in ways that alter the macromolecules' biochemical or biophysical activities. This idea, more than a century old, is embodied in the term **receptor**: the component of a cell or organism that interacts with a drug and initiates the chain of events leading to the drug's observed effects.

Receptors have become the central focus of investigation of drug effects and their mechanisms of action (pharmacodynamics). The receptor concept, extended to endocrinology, immunology, and molecular biology, has proved essential for explaining many aspects of biologic regulation. Many drug receptors have been isolated and characterized in detail, thus opening the way to precise understanding of the molecular basis of drug action.

The receptor concept has important practical consequences for the development of drugs and for arriving at therapeutic decisions in clinical practice. These consequences form the basis for understanding the actions and clinical uses of drugs described in almost every chapter of this book. They may be briefly summarized as follows:

1. **Receptors largely determine the quantitative relations between dose or concentration of drug and pharmacologic effects.** The receptor's affinity for binding a drug determines the concentration of drug required to form a significant number of drug-receptor complexes, and the total number of receptors may limit the maximal effect a drug may produce.
2. **Receptors are responsible for selectivity of drug action.** The molecular size, shape, and electrical charge of a drug determine whether—and with what affinity—it will bind to a particular receptor among the vast array of chemically different binding sites available in a cell, tissue, or patient. Accordingly, changes in the chemical structure of a drug can dramatically increase or decrease a new drug's affinities for different classes of receptors, with resulting alterations in therapeutic and toxic effects.
3. **Receptors mediate the actions of pharmacologic agonists and antagonists.** Some drugs and many natural ligands, such as hormones and neurotransmitters, regulate the function of receptor macromolecules as **agonists**; this means that they activate the receptor to signal as a direct result of binding to it. Some agonists activate a single kind of receptor to produce all their biologic functions, whereas others selectively promote one receptor function more than another.

Other drugs act as pharmacologic **antagonists**; that is, they bind to receptors but do not activate generation of a signal; consequently, they interfere with the ability of an agonist to activate the receptor. Some of the most useful drugs in clinical medicine are pharmacologic antagonists. Still other drugs bind to a different site on the receptor than that bound by endogenous ligands; such drugs can produce useful and quite different clinical effects

by acting as so-called **allosteric modulators** of the receptor.

## MACROMOLECULAR NATURE OF DRUG RECEPTORS

Most receptors for clinically relevant drugs, and nearly all of those discussed in this chapter, are proteins. Traditionally, drug binding was used to identify or purify receptor proteins from tissue extracts; consequently, receptors were discovered after the drugs that bind to them. Advances in molecular biology and genome sequencing made it possible to identify receptors by predicted structural homology to other (previously known) receptors. This effort revealed that many known drugs bind to a larger diversity of receptors than previously anticipated and motivated efforts to develop increasingly selective drugs. It also identified **orphan receptors**, so-called because their natural ligands are presently unknown; these may prove to be useful targets for future drug development.

The best-characterized drug receptors are **regulatory proteins** that mediate the actions of endogenous chemical signals such as neurotransmitters, autacoids, and hormones. This class of receptors mediates the effects of many of the most useful therapeutic agents. The molecular structures and biochemical mechanisms of these regulatory receptors are described in a later section entitled Signaling Mechanisms & Drug Action.

Other classes of proteins have been clearly identified as drug receptors. **Enzymes** may be inhibited (or, less commonly, activated) by binding a drug. Examples include dihydrofolate reductase, the receptor for the antineoplastic drug **methotrexate**; 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the receptor for statins; and various protein and lipid kinases. **Transport proteins** can be useful drug targets. Examples include Na<sup>+</sup>/K<sup>+</sup>-ATPase, the membrane receptor for cardioactive digitalis glycosides; **norepinephrine** and serotonin transporter proteins that are membrane receptors for antidepressant drugs; and **dopamine** transporters that are membrane receptors for **cocaine** and a number of other psychostimulants. **Structural proteins** are also important drug targets, such as tubulin, the receptor for the anti-inflammatory agent **colchicine**.

This chapter deals with three aspects of drug receptor function, presented in increasing order of complexity: (1) receptors as determinants of the quantitative relation between the concentration of a drug and the pharmacologic response, (2) receptors as regulatory proteins and components of chemical signaling mechanisms that provide targets for important drugs, and (3) receptors as key determinants of the therapeutic and toxic effects of drugs in patients.

## RELATION BETWEEN DRUG CONCENTRATION & RESPONSE

The relation between dose of a drug and the clinically observed response may be complex. In carefully controlled in vitro systems, however, the relation between concentration of a drug and its effect is often simple and can be described with mathematical precision. It is important to understand this idealized relation in some detail because it underlies the more complex relations between dose and effect that occur when drugs are given to patients.

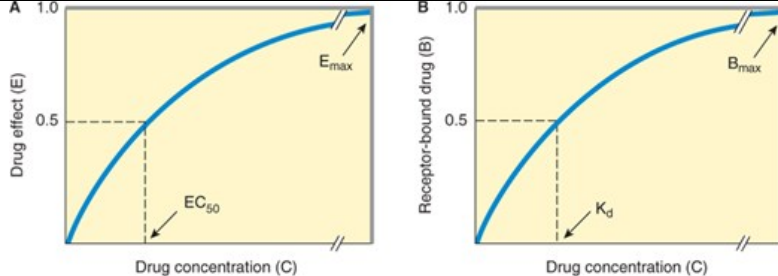
### Concentration-Effect Curves & Receptor Binding of Agonists

Even in intact animals or patients, responses to low doses of a drug usually increase in direct proportion to dose. As doses increase, however, the response increment diminishes; finally, doses may be reached at which no further increase in response can be achieved. This relation between drug concentration and effect is traditionally described by a hyperbolic curve (Figure 2-1A) according to the following equation:

$$E = \frac{E_{\max} \times C}{C + EC_{50}}$$

FIGURE 2-1

Relations between drug concentration and drug effect (A) or receptor-bound drug (B). The drug concentrations at which effect or receptor occupancy is half-maximal are denoted by **EC<sub>50</sub>** and **K<sub>d</sub>**, respectively.



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where E is the effect observed at concentration C,  $E_{max}$  is the maximal response that can be produced by the drug, and  $EC_{50}$  is the concentration of drug that produces 50% of maximal effect.

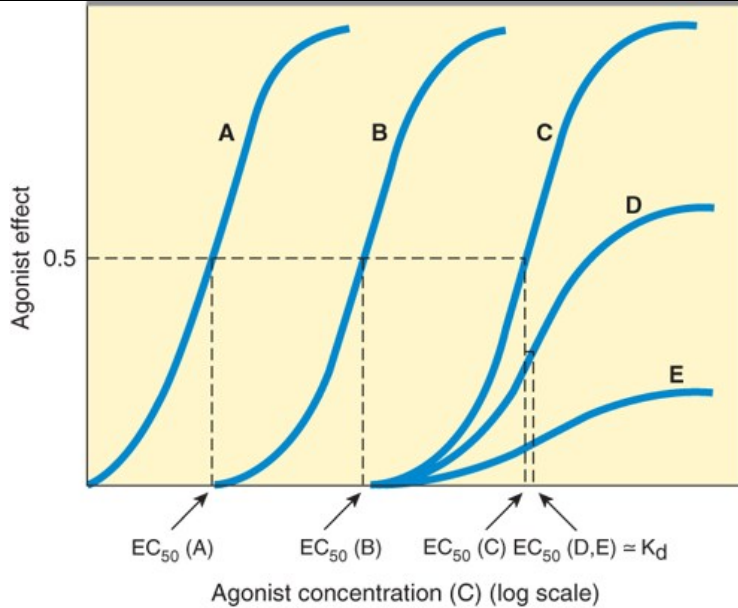
This hyperbolic relation resembles the mass action law that describes the association between two molecules of a given affinity. This resemblance suggests that drug agonists act by binding to (“occupying”) a distinct class of biologic molecules with a characteristic affinity for the drug. Radioactive receptor ligands have been used to confirm this occupancy assumption in many drug-receptor systems. In these systems, drug bound to receptors (B) relates to the concentration of free (unbound) drug (C) as depicted in Figure 2-1B and as described by an analogous equation:

$$B = \frac{B_{max} \times C}{C + K_d}$$

in which  $B_{max}$  indicates the total concentration of receptor sites (ie, sites bound to the drug at infinitely high concentrations of free drug) and  $K_d$  (the equilibrium dissociation constant) represents the concentration of free drug at which half-maximal binding is observed. This constant characterizes the receptor’s affinity for binding the drug in a reciprocal fashion: If the  $K_d$  is low, binding affinity is high, and vice versa. The  $EC_{50}$  and  $K_d$  may be identical but need not be, as discussed below. Dose-response data are often presented as a plot of the drug effect (ordinate) against the *logarithm* of the dose or concentration (abscissa), transforming the hyperbolic curve of Figure 2-1 into a sigmoid curve with a linear midportion (eg, Figure 2-2). This transformation is convenient because it expands the scale of the concentration axis at low concentrations (where the effect is changing rapidly) and compresses it at high concentrations (where the effect is changing slowly), but otherwise has no biologic or pharmacologic significance.

FIGURE 2-2

Logarithmic transformation of the dose axis and experimental demonstration of spare receptors, using different concentrations of an irreversible antagonist. Curve A shows agonist response in the absence of antagonist. After treatment with a low concentration of antagonist (curve B), the curve is shifted to the right. Maximal responsiveness is preserved, however, because the remaining available receptors are still in excess of the number required. In curve C, produced after treatment with a larger concentration of antagonist, the available receptors are no longer “spare”; instead, they are just sufficient to mediate an undiminished maximal response. Still higher concentrations of antagonist (curves D and E) reduce the number of available receptors to the point that maximal response is diminished. The apparent  $EC_{50}$  of the agonist in curves D and E may approximate the  $K_d$  that characterizes the binding affinity of the agonist for the receptor.



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## Receptor-Effector Coupling & Spare Receptors

When an agonist occupies a receptor, conformational changes occur in the receptor protein that represent the fundamental basis of receptor activation and the first of often many steps required to produce a pharmacologic response. The overall transduction process that links drug occupancy of receptors and pharmacologic response is called **coupling**. The relative efficiency of occupancy-response coupling is determined, in part, at the receptor itself; full agonists tend to shift the conformational equilibrium of receptors more strongly than partial agonists (described in the text that follows). Coupling is also determined by “downstream” biochemical events that transduce receptor occupancy into cellular response. For some receptors, such as ligand-gated ion channels, the relationship between drug occupancy and response can be simple because the ion current produced by a drug is often directly proportional to the number of receptors (ion channels) bound. For other receptors, such as those linked to enzymatic signal transduction cascades, the occupancy-response relationship is often more complex because the biologic response reaches a maximum before full receptor occupancy is achieved.

Many factors can contribute to nonlinear occupancy-response coupling, and often these factors are only partially understood. A useful concept for thinking about this is that of **receptor reserve** or **spare receptors**. Receptors are said to be “spare” for a given pharmacologic response if it is possible to elicit a maximal biologic response at a concentration of agonist that does not result in occupancy of all the available receptors. Experimentally, spare receptors may be demonstrated by using irreversible antagonists to prevent binding of agonist to a proportion of available receptors and showing that high concentrations of agonist can still produce an undiminished maximal response (see [Figure 2-2](#)). For example, the same maximal inotropic response of heart muscle to catecholamines can be elicited even when 90% of  $\beta$  adrenoceptors to which they bind are occupied by a quasi-irreversible antagonist. Accordingly, myocardial cells are said to contain a large proportion of spare  $\beta$  adrenoceptors.

What accounts for the phenomenon of spare receptors? In some cases, receptors may be simply *spare in number* relative to the total number of downstream signaling mediators present in the cell, so that a maximal response occurs without occupancy of all receptors. In other cases, “spareness” of receptors appears to be *temporal*. For example,  $\beta$ -adrenoceptor activation by an agonist promotes binding of guanosine triphosphate (GTP) to a trimeric G protein, producing an activated signaling intermediate whose lifetime may greatly outlast the agonist-receptor interaction (see also the [section G Proteins & Second Messengers](#)). Here, maximal response is elicited by activation of relatively few receptors because the response initiated by an individual ligand-receptor-binding event persists longer than the binding event itself. Irrespective of the biochemical basis of receptor reserve, the sensitivity of a cell or tissue to a particular concentration of agonist depends not only on the *affinity* of the receptor for binding the agonist (characterized by the  $K_d$ ) but also on the *degree of spareness*—the total number of receptors present compared with the number actually necessary to elicit a maximal biologic response.

The concept of spare receptors is very useful clinically because it allows one to think precisely about the effects of drug dosage without having to consider (or even fully understand) biochemical details of the signaling response. The  $K_d$  of the agonist-receptor interaction determines what fraction ( $B/B_{\max}$ ) of total receptors will be occupied at a given free concentration ( $C$ ) of agonist regardless of the receptor concentration:

$$\frac{B}{B_{\max}} = \frac{C}{C + K_d}$$

Imagine a responding cell with 100 receptors and 100 effectors. Here the number of effectors does not limit the maximal response, and the receptors are *not* spare in number. Consequently, an agonist that is present at a concentration equal to the  $K_d$  will occupy 50% of the receptors, and half of the effectors will be activated, producing a half-maximal response (ie, 50 receptors stimulate 50 effectors). Now imagine that the number of receptors increases tenfold to 1000 receptors but the total number of effectors remains constant. Most of the receptors are now spare in number. As a result, a much lower concentration of agonist suffices to occupy 50 of the 1000 receptors (5% of the receptors), and this same low concentration of agonist elicits a half-maximal response (50 of 100 effectors activated). Thus, it is possible to change the sensitivity of tissues with spare receptors by changing receptor number.

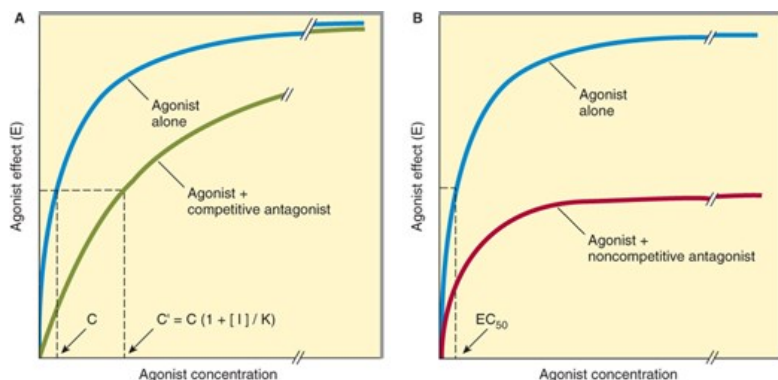
## Competitive & Irreversible Antagonists

Receptor antagonists bind to receptors but do not activate them; the primary action of antagonists is to reduce the effects of agonists (other drugs or endogenous regulatory molecules) that normally activate receptors. While antagonists are traditionally thought to have no functional effect in the absence of an agonist, some antagonists exhibit “inverse agonist” activity (see [Chapter 1](#)) because they also reduce receptor activity below basal levels observed in the absence of any agonist at all. Antagonist drugs are further divided into two classes depending on whether they act *competitively* or *noncompetitively* relative to an agonist present at the same time.

In the presence of a fixed concentration of agonist, increasing concentrations of a **competitive antagonist** progressively inhibit the agonist response; high antagonist concentrations prevent the response almost completely. Conversely, sufficiently high concentrations of agonist can surmount the effect of a given concentration of the antagonist; that is, the  $E_{\max}$  for the agonist remains the same for any fixed concentration of antagonist ([Figure 2-3A](#)). Because the antagonism is competitive, the presence of antagonist increases the agonist concentration required for a given degree of response, and so the agonist concentration-effect curve is shifted to the right.

FIGURE 2-3

Changes in agonist concentration-effect curves produced by a competitive antagonist (**A**) or by an irreversible antagonist (**B**). In the presence of a competitive antagonist, higher concentrations of agonist are required to produce a given effect; thus the agonist concentration ( $C'$ ) required for a given effect in the presence of concentration  $[I]$  of an antagonist is shifted to the right, as shown. High agonist concentrations can overcome inhibition by a competitive antagonist. This is not the case with an irreversible (or noncompetitive) antagonist, which reduces the maximal effect the agonist can achieve, although it may not change its  $EC_{50}$ .



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The concentration ( $C'$ ) of an agonist required to produce a given effect in the presence of a fixed concentration ( $[I]$ ) of competitive antagonist is greater than the agonist concentration ( $C$ ) required to produce the same effect in the absence of the antagonist. The ratio of these two agonist concentrations

(called the dose ratio) is related to the dissociation constant ( $K_i$ ) of the antagonist by the **Schild equation**:

$$\frac{C'}{C} = 1 + \frac{[I]}{K_i}$$

Pharmacologists often use this relation to determine the  $K_i$  of a competitive antagonist. Even without knowledge of the relation between agonist occupancy of the receptor and response, the  $K_i$  can be determined simply and accurately. As shown in [Figure 2-3](#), concentration-response curves are obtained in the presence and in the absence of a fixed concentration of competitive antagonist; comparison of the agonist concentrations required to produce identical degrees of pharmacologic effect in the two situations reveals the antagonist's  $K_i$ . If  $C'$  is twice  $C$ , for example, then  $[I] = K_i$ .

For the clinician, this mathematical relation has two important therapeutic implications:

1. The degree of inhibition produced by a competitive antagonist depends on the concentration of antagonist. The competitive  $\beta$ -adrenoceptor antagonist [propranolol](#) provides a useful example. Patients receiving a fixed dose of this drug exhibit a wide range of plasma concentrations, owing to differences among individuals in the clearance of [propranolol](#). As a result, inhibitory effects on physiologic responses to [norepinephrine](#) and [epinephrine](#) (endogenous adrenergic receptor agonists) may vary widely, and the dose of [propranolol](#) must be adjusted accordingly.
2. Clinical response to a competitive antagonist also depends on the concentration of agonist that is competing for binding to receptors. Again, [propranolol](#) provides a useful example: When this drug is administered at moderate doses sufficient to block the effect of basal levels of the neurotransmitter [norepinephrine](#), resting heart rate is decreased. However, the increase in the release of [norepinephrine](#) and [epinephrine](#) that occurs with exercise, postural changes, or emotional stress may suffice to overcome this competitive antagonism. Accordingly, the same dose of [propranolol](#) may have little effect under these conditions, thereby altering therapeutic response. Conversely, the same dose of [propranolol](#) that is useful for treatment of hypertension in one patient may be excessive and toxic to another, based on differences between the patients in the amount of endogenous [norepinephrine](#) and [epinephrine](#) that they produce.

The actions of a **noncompetitive antagonist** are different because, once a receptor is bound by such a drug, agonists cannot surmount the inhibitory effect irrespective of their concentration. In many cases, noncompetitive antagonists bind to the receptor in an **irreversible** or nearly irreversible fashion, sometimes by forming a covalent bond with the receptor. After occupancy of some proportion of receptors by such an antagonist, the number of remaining unoccupied receptors may be too low for the agonist (even at high concentrations) to elicit a response comparable to the previous maximal response ([Figure 2-3B](#)). If spare receptors are present, however, a lower dose of an irreversible antagonist may leave enough receptors unoccupied to allow achievement of maximum response to agonist, although a higher agonist concentration will be required ([Figures 2-2B](#) and [2-2C](#); see section [Receptor-Effector Coupling & Spare Receptors](#)).

Therapeutically, such irreversible antagonists present distinct advantages and disadvantages. Once the irreversible antagonist has occupied the receptor, it need not be present in unbound form to inhibit agonist responses. Consequently, the duration of action of such an irreversible antagonist is relatively independent of its own rate of elimination and more dependent on the rate of turnover of receptor molecules.

[Phenoxybenzamine](#), an irreversible  $\alpha$ -adrenoceptor antagonist, is used to control the hypertension caused by catecholamines released from pheochromocytoma, a tumor of the adrenal medulla. If administration of [phenoxybenzamine](#) lowers blood pressure, blockade will be maintained even when the tumor episodically releases very large amounts of catecholamine. In this case, the ability to prevent responses to varying and high concentrations of agonist is a therapeutic advantage. If overdose occurs, however, a real problem may arise. If the  $\alpha$ -adrenoceptor blockade cannot be overcome, excess effects of the drug must be antagonized “physiologically,” ie, by using a pressor agent that does not act via  $\alpha$  adrenoceptors.

Antagonists can function noncompetitively in a different way; that is, by binding to a site on the receptor protein separate from the agonist binding site; in this way, the drug can modify receptor activity without blocking agonist binding (see [Chapter 1](#), [Figures 1-2C](#) and [1-2D](#)). Although these drugs act noncompetitively, their actions are often reversible. Such drugs are called *negative allosteric modulators* because they act through binding to a different (ie, “allosteric”) site on the receptor relative to the classical (ie, “orthosteric”) site bound by the endogenous agonist to reduce activity of the receptor. Other allosteric modulators have the opposite effect: they increase receptor activity. Benzodiazepine drugs like [diazepam](#), for example, bind to an allosteric site on ion channels that are physiologically activated by the neurotransmitter  $\gamma$ -aminobutyric acid (GABA). Benzodiazepines are considered *positive allosteric modulators* of GABA receptors because they potentiate (rather than inhibit) the ability of the orthosteric agonist (GABA) to increase channel conductance. A useful feature of this allosteric mechanism is that benzodiazepines have little activating effect on their own. This contributes to making benzodiazepines relatively safe in overdose unless combined with other sedating drugs. The concept of allosteric modulators

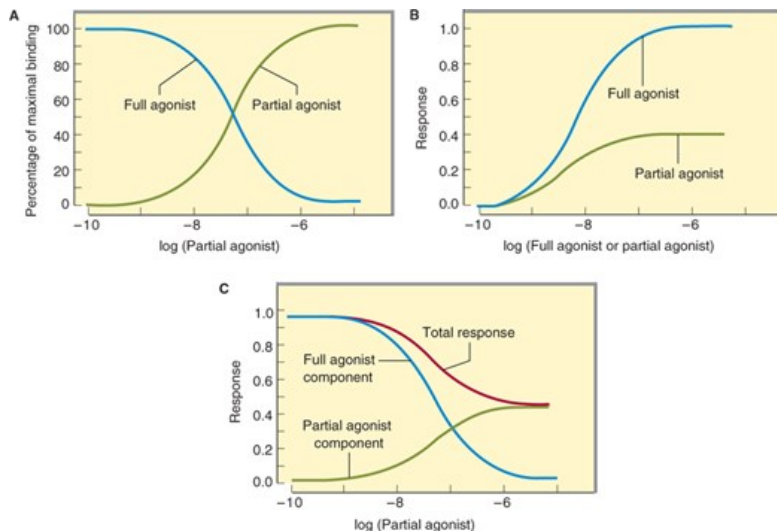
also applies to proteins that lack any known physiological binding site. For example, **ivacaftor** binds to the **cystic fibrosis transmembrane regulator (CFTR)** ion channel that is mutated in cystic fibrosis. Some mutations that cause disease by rendering this channel hypoactive can be partially rescued by **ivacaftor**, despite CFTR having no known physiological agonist—and thus no (presently recognized) orthosteric binding site.

## Partial Agonists

Based on the maximal pharmacologic response that occurs when all receptors are occupied, agonists can be divided into two classes: **partial agonists** produce a lower response, at full receptor occupancy, than do **full agonists**. Partial agonists produce concentration-effect curves that resemble those observed with full agonists in the presence of an antagonist that irreversibly blocks some of the receptor sites (compare **Figures 2-2** [curve D] and **2-4B**). It is important to emphasize that the failure of partial agonists to produce a maximal response is not due to decreased affinity for binding to receptors. Indeed, a partial agonist's inability to cause a maximal pharmacologic response, even when present at high concentrations that effectively saturate binding to all receptors, is indicated by the fact that partial agonists competitively inhibit the responses produced by full agonists (**Figure 2-4**). This mixed “agonist-antagonist” property of partial agonists can have both beneficial and deleterious effects in the clinic. For example, **buprenorphine**, a partial agonist of  $\mu$ -opioid receptors, is a generally safer analgesic drug than **morphine**, a more efficacious partial agonist, and much safer than **fentanyl** which is a full agonist. This is because **buprenorphine** suppresses breathing upon binding opioid receptors (in ventilatory pacemaker neurons of the brainstem) less strongly than **morphine**, and much less strongly than **fentanyl**; breathing stops if these receptors are activated too strongly. On the other hand, **buprenorphine** is effectively antianalgesic when administered in combination with more efficacious opioid drugs, due to the mixed agonist-antagonist effect. In addition, **buprenorphine** may precipitate a severe drug withdrawal reaction in opioid-dependent individuals, due to physiologic adaptations of the nervous system that are induced after prolonged or repeated drug exposure and effectively change the “set point” for sensitivity to opioids.

**FIGURE 2-4**

**A:** The percentage of receptor occupancy resulting from full agonist (present at a single concentration) binding to receptors in the presence of increasing concentrations of a partial agonist. Because the full agonist (blue line) and the partial agonist (green line) compete to bind to the same receptor sites, when occupancy by the partial agonist increases, binding of the full agonist decreases. **B:** When each of the two drugs is used alone and response is measured, occupancy of all the receptors by the partial agonist produces a lower maximal response than does similar occupancy by the full agonist. **C:** Simultaneous treatment with a single concentration of full agonist and increasing concentrations of the partial agonist produces the response patterns shown in the bottom panel. The fractional response caused by a single high concentration of the full agonist decreases as increasing concentrations of the partial agonist compete to bind to the receptor with increasing success; at the same time, the portion of the response caused by the partial agonist increases, while the total response—ie, the sum of responses to the two drugs (red line)—gradually decreases, eventually reaching the value produced by partial agonist alone (compare with B).



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## Other Mechanisms of Drug Antagonism

Not all mechanisms of antagonism involve interactions of drugs or endogenous ligands at a single type of receptor, and some types of antagonism do not involve a receptor protein at all. For example, **protamine**, a protein that is positively charged at physiologic pH, can be used clinically as a drug to counteract the effects of **heparin**, a nonprotein (glycosaminoglycan) anticoagulant drug that is negatively charged. In this case, one drug acts as a **chemical antagonist** of the other simply by ionic binding that makes the other drug unavailable to interact with proteins involved in blood clotting.

Another type of antagonism is **physiologic antagonism** between endogenous regulatory pathways mediated by different receptors. For example, several catabolic actions of the glucocorticoid hormones lead to increased blood glucose levels, an effect that is physiologically opposed by **insulin**. Although glucocorticoids and **insulin** act on quite distinct receptor-effector systems, the clinician must sometimes administer **insulin** to oppose the hyperglycemic effects of a glucocorticoid hormone, whether the latter is elevated by endogenous synthesis (eg, a tumor of the adrenal cortex) or as a result of glucocorticoid therapy.

In general, use of a drug as a physiologic antagonist produces effects that are less specific and less easy to control than are the effects of a receptor-specific antagonist. Thus, for example, to treat bradycardia caused by increased release of **acetylcholine** from vagus nerve endings, the clinician could use **isoproterenol**, a  $\beta$ -adrenoceptor agonist that increases heart rate by mimicking sympathetic stimulation of the heart. However, use of this physiologic antagonist would be less rational—and potentially more dangerous—than a receptor-specific antagonist such as **atropine**.

## SIGNALING MECHANISMS & DRUG ACTION

Until now we have considered receptor interactions and drug effects in terms of equations and concentration-effect curves. We must also understand the molecular mechanisms by which drugs act. We should also consider different structural families of receptor proteins, and this allows us to ask basic questions with important clinical implications:

- Why do some drugs produce effects that persist for minutes, hours, or even days after the drug is no longer present?
- Why do responses to other drugs diminish rapidly with prolonged or repeated administration?
- How do cellular mechanisms for amplifying external chemical signals explain the phenomenon of spare receptors?
- Why do chemically similar drugs often exhibit extraordinary selectivity in their actions?
- Do these mechanisms provide targets for developing new drugs?

Most transmembrane signaling is accomplished by a small number of different molecular mechanisms. Each type of mechanism has been adapted, through the evolution of distinctive protein families, to transduce many different signals. These protein families include receptors on the cell surface and within the cell, as well as enzymes and other components that generate, amplify, coordinate, and terminate postreceptor signaling by nonprotein chemical mediators in the cell that are collectively called **second messengers**. This section first discusses mechanisms for carrying chemical information across the plasma membrane and then discusses some examples of second messenger chemicals.

Five basic mechanisms of transmembrane signaling are well understood (Figure 2–5). Each represents a different family of receptor protein and uses a different strategy to circumvent the barrier posed by the lipid bilayer of the plasma membrane. These strategies use (1) a lipid-soluble ligand that crosses the membrane and acts on an intracellular receptor; (2) a transmembrane receptor protein whose intracellular enzymatic activity is allosterically regulated by a ligand that binds to a site on the protein's extracellular domain; (3) a transmembrane receptor that binds and stimulates an intracellular protein tyrosine kinase; (4) a ligand-gated transmembrane ion channel that can be induced to open or close by the binding of a ligand; and (5) a transmembrane receptor protein that stimulates a GTP-binding signal transducer protein (G protein), which in turn modulates production of an intracellular second messenger.

FIGURE 2–5

Known transmembrane signaling mechanisms: **1**: A lipid-soluble chemical signal crosses the plasma membrane and acts on an intracellular receptor (which may be an enzyme or a regulator of gene transcription); **2**: the signal binds to the extracellular domain of a transmembrane protein, thereby activating an enzymatic activity of its cytoplasmic domain; **3**: the signal binds to the extracellular domain of a transmembrane receptor bound to a separate protein tyrosine kinase, which it activates; **4**: the signal binds to and directly regulates the opening of an ion channel; **5**: the signal binds to a