Bertram G. Katzung
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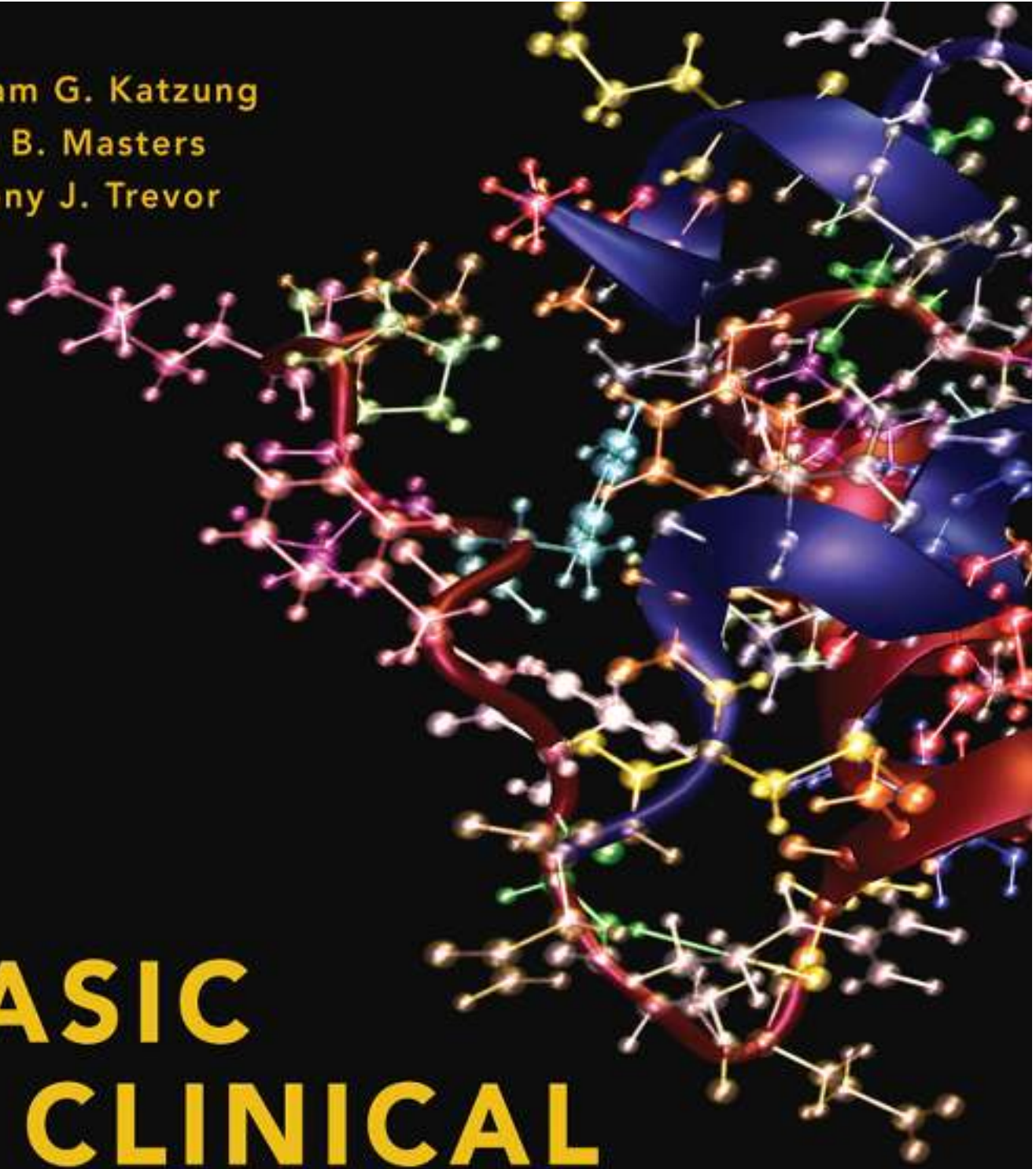

BASIC & CLINICAL PHARMACOLOGY

12th Edition

Mc Graw Hill LANGE™

SCHEDULE OF CONTROLLED DRUGS[1]

SCHEDULE I

(All nonresearch use illegal under federal law.)

Flunitrazepam (Rohypnol)

Narcotics:

Heroin and many nonmarketed synthetic narcotics

Hallucinogens:

LSD

MDA, STP, DMT, DET, mescaline, peyote, bufotenine, ibogaine, psilocybin, phencyclidine (PCP; veterinary drug only)

Marijuana

Methaqualone

SCHEDULE II

(No telephone prescriptions, no refills.)[2]

Opioids:

Opium

Opium alkaloids and derived phenanthrene alkaloids: codeine, morphine, (Avinza, Kadian, MSContin, Roxanol), hydromorphone (Dilaudid), oxymorphone (, Exalgo), oxycodone (dihydroxycodeinone, a component of Oxycontin, Percodan, Percocet, Roxicodone, Tylox)

Designated synthetic drugs: meperidine (Demerol), methadone, levorphanol (Levo-Dromoran), fentanyl (Duragesic, Actiq, Fentora), alfentanil (Alfenta), sufentanil (Sufenta), remifentanil (Ultiva), tapentadol (Nycynta)

Stimulants:

Coca leaves and cocaine

Amphetamine

Amphetamine complex (Biphetamine)

Amphetamine salts (Adderall)

Dextroamphetamine (Dexedrine, Procentra)

Lisdexamfetamine (Vyvanse)

Methamphetamine (Desoxyn)

Methylphenidate (Ritalin, Concerta, Methylin, Daytrana, Medadate)

Above in mixtures with other controlled or uncontrolled drugs

Cannabinoids:

Nabilone (Cesamet)

Depressants:

Amobarbital (Amytal)

Pentobarbital (Nembutal)

Secobarbital (Seconal)

SCHEDULE III

(Prescription must be rewritten after 6 months or five refills.)

Opioids:

Buprenorphine (Buprenex, Subutex)

Mixture of above Buprenorphine and Naloxone (Suboxone)

The following opioids in combination with one or more active non-opioid ingredients, provided the amount does not exceed that shown:

Codeine and dihydrocodeine: not to exceed 1800 mg/dL or 90 mg/tablet or other dosage unit

Dihydrocodeinone (hydrocodone in Hycodan, Vicodin, and Lortab): not to exceed 300 mg/dL or 15 mg/tablet

Opium: 500 mg/dL or 25 mg/5 mL or other dosage unit (paregoric)

Stimulants:

Benzphetamine (Didrex)

Phendimetrazine (Bontril)

Depressants:

Schedule II barbiturates in mixtures with noncontrolled drugs or in suppository dosage form

Butabarbital (Butisol)

Ketamine (Ketalar)

Cannabinoids:

Dronabinol (Marinol)

Anabolic Steroids:

Fluoxymesterone (Androxy)

Methyltestosterone (Android, Testred, Methitest)

Nandrolone decanoate (Deca-Durabolin) Non US

Nandrolone phenpropionate (Durabolin) Non US

Oxandrolone (Oxandrin), Oxymetholone (Androl-50)

Stanozolol (Winstrol),

Testolactone (Teslac),

Testosterone and its esters

SCHEDULE IV

(Prescription must be rewritten after 6 months or five refills; differs from Schedule III in penalties for illegal possession.)

Opioids:

Butorphanol (Stadol)

Difenoxin 1 mg + atropine 25 mcg (Motofen)

Pentazocine (Talwin)

Stimulants:

Armodafinil (Nuvigil)

Diethylpropion (Tenuate) not in US

Modafinil (Provigil)

Phentermine (Ionamin, Adipex-P)

Depressants:

Benzodiazepines

Alprazolam (Xanax)

Chlordiazepoxide (Librium)

Clonazepam (Klonopin)

Clorazepate (Tranxene)

Diazepam (Valium)

Estazolam (ProSom)

Flurazepam (Dalmane)

Halazepam (Paxipam)

Lorazepam (Ativan)

Midazolam (Versed)

Oxazepam (Serax)

Prazepam (Centrax)

Quazepam (Doral)

Temazepam (Restoril)

Triazolam (Halcion)

Chloral hydrate (Somnote)

Eszopiclone (Lunesta)

Meprobamate (Equanil, Miltown, etc)

Methobarbital (Mebaral)

Methohexital (Brevital)

Paraldehyde

Phenobarbital

Zaleplon (Sonata)

Zolpidem (Ambien)

SCHEDULE V

(As any other nonopioid prescription drug)

Codeine: 200 mg/100 mL

Difenoxin preparations: 0.5 mg + 25 mcg atropine

Dihydrocodeine preparations: 10 mg/100 mL

Diphenoxylate (not more than 2.5 mg and not less than 0.025 mg of atropine per dosage unit, as in Lomotil)

Ethylmorphine preparations: 100 mg/100 mL

Opium preparations: 100 mg/100 mL

Pregabalin (Lyrica)

Pyrovalerone (Centroton, Thymergix)

[1]See http://*www.usdoj.gov/dea/pubs/scheduling.html* for additional details.

[2]Emergency prescriptions may be telephoned if followed within 7 days by a valid written prescription annotated to indicate that it was previously placed by telephone.

a LANGE medical book

Basic & Clinical Pharmacology

Twelfth Edition

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Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

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Preface

The twelfth edition of *Basic & Clinical Pharmacology* continues the important changes inaugurated in the eleventh edition, with extensive use of full-color illustrations and expanded coverage of transporters, pharmacogenomics, and new drugs. Case studies have been added to several chapters and answers to questions posed in the case studies now appear at the end of each chapter. As in prior editions, the book is designed to provide a comprehensive, authoritative, and readable pharmacology textbook for students in the health sciences. Frequent revision is necessary to keep pace with the rapid changes in pharmacology and therapeutics; the 2–3 year revision cycle of the printed text is among the shortest in the field and the availability of an online version provides even greater currency. In addition to the full-color illustrations, other new features have been introduced. The Case Study Answer section at the end of chapters will make the learning process even more interesting and efficient. The book also offers special features that make it a useful reference for house officers and practicing clinicians.

Information is organized according to the sequence used in many pharmacology courses and in integrated curricula: basic principles; 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.

Major features that make this book particularly useful in integrated 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 commercial preparations available, including trade and generic names and dosage formulations, are provided at the end of each chapter for easy reference by the house officer or practitioner writing a chart order or prescription.

Significant revisions in this edition include:

- In addition to the Case Studies used to open many chapters, Case Study Answers at the end of these chapters provide an introduction to the clinical applications of the drugs discussed.
- A Drug Summary Table is placed at the conclusion of most chapters; these provide a concise recapitulation of the most important drugs.
- Many new illustrations in full color provide significantly more information about drug mechanisms and effects and help to clarify important concepts.
- Major revisions of the chapters on sympathomimetic, sympathoplegic, antipsychotic, antidepressant, antidiabetic, anti-inflammatory, and antiviral drugs, prostaglandins, nitric oxide, hypothalamic and pituitary hormones, and immunopharmacology.
- Continued expansion of the coverage of general concepts relating to newly discovered receptors, receptor mechanisms, and drug transporters.
- Descriptions of important new drugs released through August 2011.

An important related educational resource is *Katzung & Trevor's Pharmacology: Examination & Board Review,* ninth edition (Trevor AJ, Katzung BG, & Masters SB: McGraw-Hill, 2010). This book provides a succinct review of pharmacology with over one thousand 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,* second edition (Katzung BG, Trevor AJ: McGraw-Hill, 2006).

This edition marks the 30th year of publication of *Basic & Clinical Pharmacology.* The widespread adoption of the first eleven editions indicates that this book fills an important need. We believe that the twelfth edition will satisfy this need even more successfully. Spanish, Portuguese, Italian, French, Indonesian, Japanese, Korean, and Turkish translations are available. Translations into other languages are under way; 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 editors for this edition, Donna Frassetto and Rachel D'Annucci Henriquez. I also wish to thank my wife, Alice Camp, for her expert proofreading contributions since the first edition.

This edition is dedicated to the memory of James Ransom, PhD, the long-time Senior Editor at Lange Medical Publications, who provided major inspiration and invaluable guidance through the first eight editions of the book. Without him, this book would not exist.

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

Bertram G. Katzung, MD, PhD
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December, 2011

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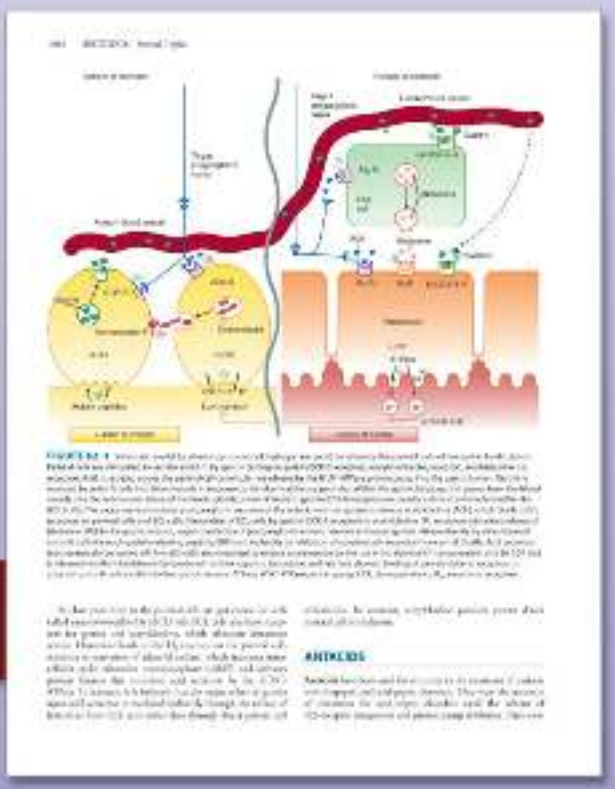
*Deceased

Key Features of *Basic & Clinical Pharmacology, 12e*

The most comprehensive, authoritative, and engaging pharmacology textbook for students in the health sciences

Key Features

- More than 300 full-color illustrations
- Emphasis is placed on discussion of drug groups and prototypes within each chapter
- NEW case studies open several chapters, adding clinical relevance to the material
- NEW case study answers at the end of the chapters provide an introduction to the clinical application of the drugs discussed
- NEW drug summary tables conclude most chapters, providing a concise summary of the most important drugs
- Expanded coverage of general concepts relating to newly discovered receptors, receptor mechanisms, and drug transporters
- Lists of the commercial preparations available, including trade and generic names and dosage formulations, are provided at the end of each chapter
- Selection of the material and order of presentation is based on the author's years of experience in teaching this material to thousands of students
- Material is organized according to the sequence used in most pharmacology courses



Hundreds of full-color illustrations enrich the text

Drug Summary Tables conclude most chapters

Case studies are included in selected chapters

Lists of the commercial preparations available appear at the end of the chapter

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SECTION I BASIC PRINCIPLES

CHAPTER 1

Introduction

Bertram G. Katzung, MD, PhD

CASE STUDY

A 26-year-old man is brought by friends to the emergency department of the city hospital because he has been behaving strangely for several days. A known user of methamphetamine, he has not eaten or slept in 48 hours. He threatened to shoot one of his friends because he believes this friend is plotting against him. On admission, the man is extremely agitated, appears to be underweight, and is unable to give a coherent history. He has to be restrained to prevent him from walking out of the emergency department and into traffic on the street. His blood pressure is 160/100 mm Hg, heart rate 100, temperature 39°C, and respirations 30/min. His arms show evidence of numerous intravenous injections. The remainder of his physical examination is unremarkable. After evaluation, the man is given a sedative, fluids, a diuretic, and ammonium chloride parenterally. What is the purpose of the ammonium chloride?

Pharmacology can be defined as the study of substances that interact with living systems through chemical processes, especially by binding 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 HISTORY OF PHARMACOLOGY

Prehistoric people undoubtedly recognized the beneficial or toxic effects of many plant and animal materials. Early written records from China and Egypt and the traditions of India list remedies of many types, including a few that are still recognized as useful drugs today. Most, however, were worthless or actually harmful. In the 1500 years or so preceding the present, there were sporadic attempts to introduce rational methods into medicine, but none was successful owing to the dominance of systems of thought 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

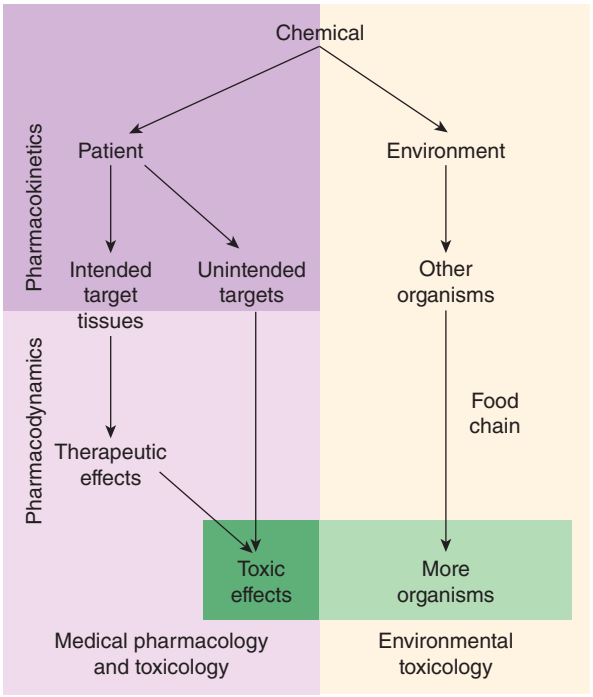

FIGURE 1–1 Major areas of study in pharmacology. The actions of chemicals can be divided into two large domains. The first (*left side*) is that of medical pharmacology and toxicology, which is aimed at understanding the actions of drugs as chemicals on individual organisms, especially humans and domestic 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.

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, and following the example of the physical sciences, reliance on observation and experimentation began to replace theorizing in 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 to the effects of traditional drugs used in their own practices. Thus, **materia medica**—the science of drug preparation and the medical use 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 later 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 tissue 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 accurately evaluate therapeutic claims.

Around the same time, 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 half-century, many fundamentally new drug groups and new members of old groups were 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 surmised. 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.

Pharmacogenomics—the relation of the individual's genetic makeup to his or her response to specific drugs—is close to becoming a practical area of therapy (see Box: Pharmacology & Genetics). 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. Discovery that small segments of RNA can interfere with protein synthesis with extreme selectivity has led to investigation of **small interfering RNAs (siRNAs)** and **microRNAs (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. These intracellular targets may provide the next major wave of advances in therapeutics.

The extension of scientific principles into everyday therapeutics is still going on, although the medication-consuming public is still exposed to vast amounts of inaccurate, incomplete, or unscientific information regarding the pharmacologic effects of chemicals. This has resulted in the irrational use of innumerable expensive, ineffective, and sometimes harmful remedies and the growth of a huge "alternative health care" industry. Unfortunately, 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 Chapter 5. 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

Pharmacology & Genetics

It has been known for centuries that certain diseases are inherited, and we now understand that individuals with such diseases have a heritable abnormality in their DNA. During the last 10 years, the genomes of humans, mice, and many other organisms have been decoded in considerable detail. This has opened the door to a remarkable range of new approaches to research and treatment. It is now possible in the case of some inherited diseases to define exactly which DNA base pairs are anomalous and in which chromosome they appear. In a small number of animal models of such diseases, it has been possible to correct the abnormality by gene therapy, ie, insertion of an appropriate "healthy" gene into somatic cells. Human somatic cell **gene therapy** has been attempted, but the technical difficulties are great.

Studies of a newly discovered receptor or endogenous ligand are often confounded by incomplete knowledge of the exact role of that receptor or ligand. One of the most powerful of the new genetic techniques is the ability to breed animals (usually mice) in which the gene for the receptor or its endogenous ligand has been "knocked out," ie, mutated so that the gene product is absent or nonfunctional. Homozygous **knockout** mice usually have complete suppression of that function, whereas heterozygous animals usually have partial suppression. Observation of the behavior, biochemistry, and physiology of the knockout mice often defines the role of the missing gene product very clearly. When the products of a particular gene are so essential that even heterozygotes do not survive to birth, it is sometimes possible to breed "knockdown" versions with only limited suppression of function. Conversely, "knockin" mice, which overexpress certain proteins of interest, have been bred.

Some patients respond to certain drugs with greater than usual sensitivity to standard doses. It is now clear that such increased sensitivity is often due to a very small genetic modification that results in decreased activity of a particular enzyme responsible for eliminating that drug. (Such variations are discussed in Chapter 4.) **Pharmacogenomics** (or pharmacogenetics) is the study of the genetic variations that cause differences in drug response among individuals or populations. Future clinicians may screen every patient for a variety of such differences before prescribing a drug.

science by a segment of the public and to a common tendency to assume that all adverse drug effects are the result of malpractice.

Two general principles that the student should remember are (1) that *all* substances can under certain circumstances be toxic, and the chemicals in botanicals (herbs and plant extracts) are no different from chemicals in manufactured drugs except for the proportion of impurities (greater in botanicals); and, (2) 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.

PHARMACOLOGY & THE PHARMACEUTICAL INDUSTRY

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 the 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 discovery and development. As described in Chapter 5, these companies are uniquely skilled in exploiting discoveries from academic and governmental laboratories and translating these basic findings into commercially successful therapeutic breakthroughs.

Such breakthroughs come at a price, however, and the escalating cost of drugs has become a significant contributor to the inflationary increase in the cost of health care. Development of new drugs is enormously expensive, and to survive and prosper, big pharma must pay the costs of drug development and marketing and return a profit to its shareholders. Today, considerable controversy surrounds drug pricing. Critics claim that the costs of development and marketing are grossly inflated by marketing activities, which may consume as much as 25% or more of a company's budget in advertising and other promotional efforts. Furthermore, profit margins for big pharma have historically exceeded all other industries by a significant factor. 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.

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 molecule in the biologic system that plays a regulatory role. This target molecule is called a **receptor**. 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 body (ie, **xenobiotics,** from the Greek *xenos*, meaning "stranger"). **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.

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 given 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.

The Physical Nature of Drugs

Drugs may be solid at room temperature (eg, aspirin, atropine), liquid (eg, nicotine, ethanol), or gaseous (eg, nitrous oxide). These factors often determine the best route of administration. The most common routes of administration are described in Table 3–3. The various classes of organic compounds—carbohydrates, proteins, lipids, and their constituents—are all represented in pharmacology. As noted above, oligonucleotides, in the form of small segments of RNA, have entered clinical trials and are on the threshold of introduction into therapeutics.

A number of useful or dangerous drugs are inorganic elements, eg, lithium, iron, and heavy metals. 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 such drugs (see text that follows).

Drug Size

The molecular size of drugs varies from very small (lithium ion, MW 7) to very large (eg, alteplase [t-PA], a protein of MW 59,050). 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 drugs must be able to move within the body (eg, from the site of administration to the site of action). Drugs much larger than MW 1000 do not diffuse readily between compartments of the body (see 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, the drug is administered directly into the vascular compartment by intravenous or intra-arterial infusion.

Drug Reactivity and 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 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 are 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 short-acting 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 receptor site via the bonds just described. Optimally, the drug's shape is complementary to that of the receptor site 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

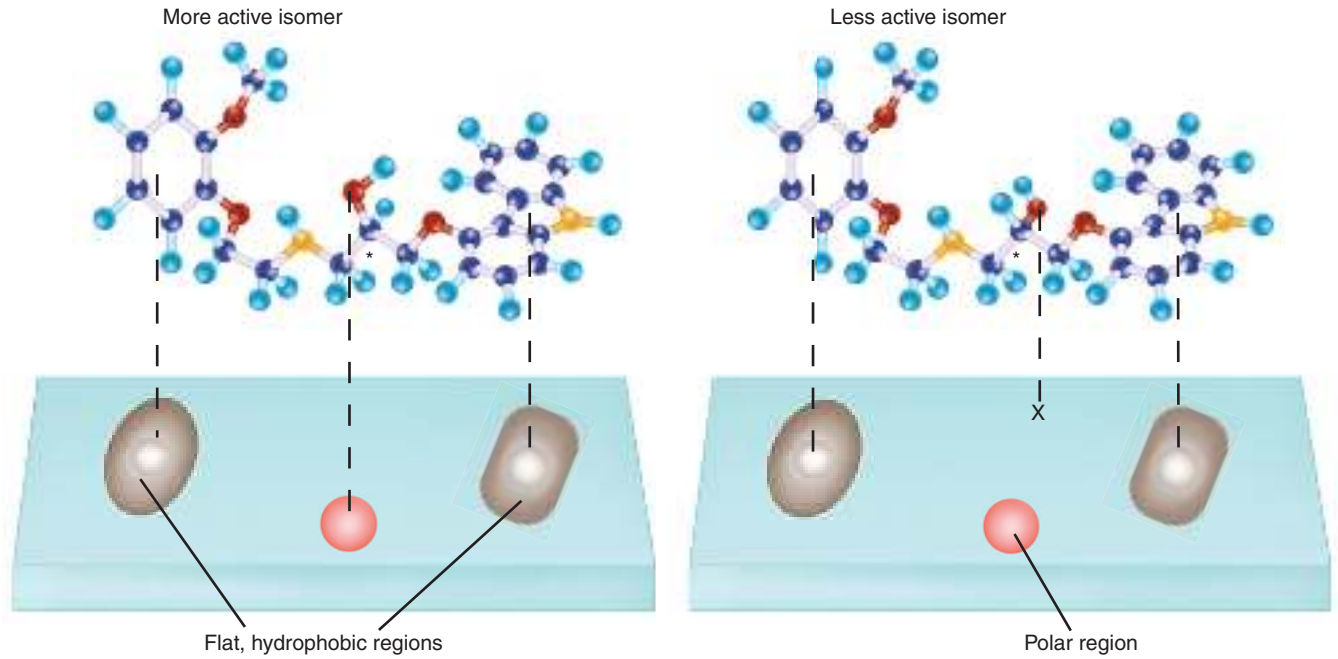

FIGURE 1–2 Cartoon illustrating the nonsuperimposibility of the two stereoisomers of carvedilol on the β receptor. The "receptor surface" has been grossly oversimplified. The chiral center carbon is denoted with an asterisk. One of the two isomers fits the three-dimensional configuration of binding site of the β-adrenoceptor molecule very well (*left*), and three groups, including an important polar moiety (an hydroxyl group, indicated by the central dashed line), bind to key areas of the surface. The less active isomer cannot orient all three binding areas to the receptor surface (*right*). (Molecule generated by means of Jmol, an open-source Java viewer for chemical structures in 3D [http://jmol.sourceforge.net/] with data from DrugBank [http://www.drugbank.ca].)

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 (Figure 1–2, Table 1–1). One of these enantiomers, the *(S)*(–) isomer, is a potent β-receptor blocker. The *(R)*(+) isomer is 100-fold weaker at the β receptor. However, the isomers are approximately equipotent as α-receptor blockers. Ketamine is an intravenous anesthetic. The (+) enantiomer is a more potent anesthetic and is less toxic than the (–) enantiomer. Unfortunately, the drug is still used as the racemic mixture.

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, only a small percentage of the chiral drugs used clinically are marketed as the active isomer—the rest are available only as racemic mixtures. As a result, many patients are receiving drug doses of which 50% is less active, inactive, or actively toxic. Some drugs are currently available in both the racemic and the pure, active isomer forms. Unfortunately, the hope that administration of the pure, active enantiomer would decrease adverse effects relative to those produced by racemic formulations has not been firmly established. However, there is increasing interest at both the scientific and the regulatory levels in making more chiral drugs available as their active enantiomers.

TABLE 1–1 Dissociation constants (K_d) of the enantiomers and racemate of carvedilol.

Form of Carvedilol	α Receptors (K_d, nmol/L[1])	β Receptors (K_d, nmol/L)
R(+) enantiomer	14	45
S(–) enantiomer	16	0.4
R,S(±) enantiomers	11	0.9

[1]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 et al: The pharmacology of carvedilol. Eur J Pharmacol 1990;38:S82.

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 (see Chapter 5). 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 to Alexander SPH, Mathie A, Peters JA: Guide to receptors and channels (GRAC), 4th edition. *Br J Pharmacol* 2009;158(Suppl 1):S1–S254. 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 (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 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 what is often a complex sequence of 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 1–3A). 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 five 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 1–3B), 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 1–3C) or inhibit (Figure 1–3D) the action of the agonist molecule. Allosteric inhibition is not overcome by increasing the dose of agonist.

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 cholinoceptor *agonist* molecules even though cholinesterase inhibitors do not bind or only incidentally bind to cholinoceptors (see Chapter 7). Because they amplify the effects of physiologically released agonist ligands, their effects are sometimes more selective and less toxic than those of exogenous agonists.

C. Agonists, Partial Agonists, and Inverse Agonists

Figure 1–4 describes a useful model of drug-receptor interaction. As indicated, the receptor is postulated to exist in the inactive,

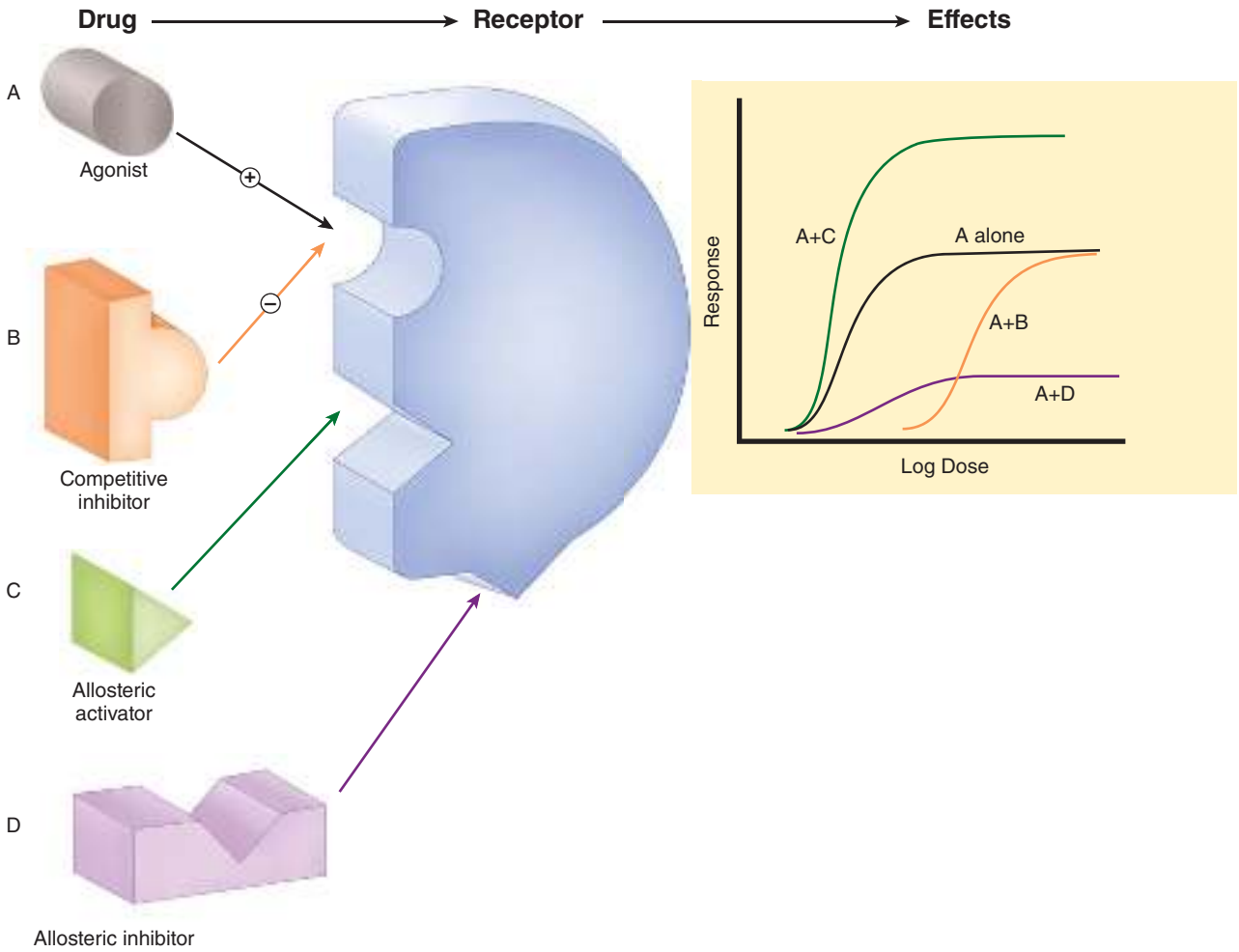

FIGURE 1–3 Drugs may interact with receptors in several ways. The effects resulting from these interactions are diagrammed in the dose-response curves at the right. Drugs that alter the agonist (**A**) response may activate the agonist binding site, compete with the agonist (competitive inhibitors, **B**), 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.

nonfunctional form (R_i) and 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 activity.** Agonists are those drugs that 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.

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 1–4, 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.** Thus, pindolol, a β-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 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.**

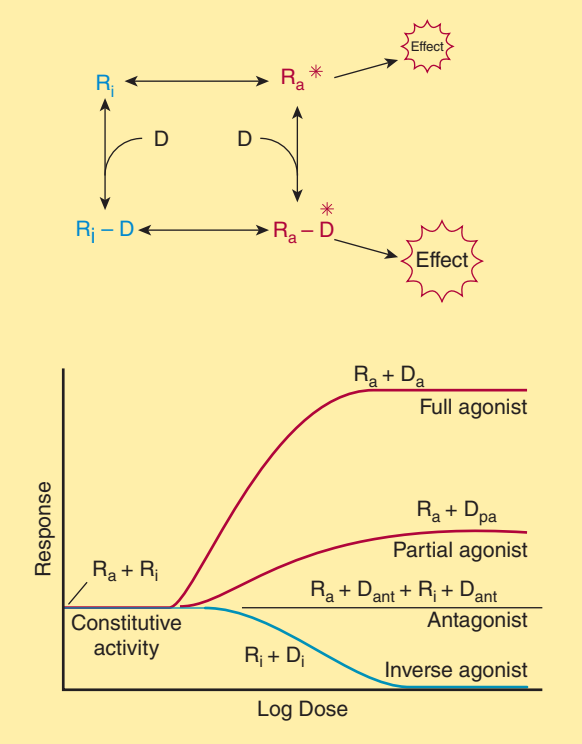

FIGURE 1–4 A model of drug-receptor interaction. The receptor is able to assume two conformations. In the R_i conformation, it is inactive and produces no effect, even when combined with a drug molecule. In the R_a conformation, the receptor can activate downstream mechanisms that produce a small observable 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.

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 would reduce any constitutive activity, thus resulting in effects that are the opposite of the effects produced by conventional agonists at that receptor. Such drugs have been termed **inverse agonists** (Figure 1–4). One of the best documented examples of such a system is the γ-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 cause GABA-like inhibition with sedation as the therapeutic result. This inhibition can be blocked by conventional neutral antagonists such as flumazenil. In addition, inverse agonists have been found that cause anxiety and agitation, the inverse of sedation (see Chapter 22). Similar inverse agonists have been found for β-adrenoceptors, histamine H_1 and H_2 receptors, and several other receptor systems.

D. Duration of Drug Action

Termination of drug action is a result of one of 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. 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