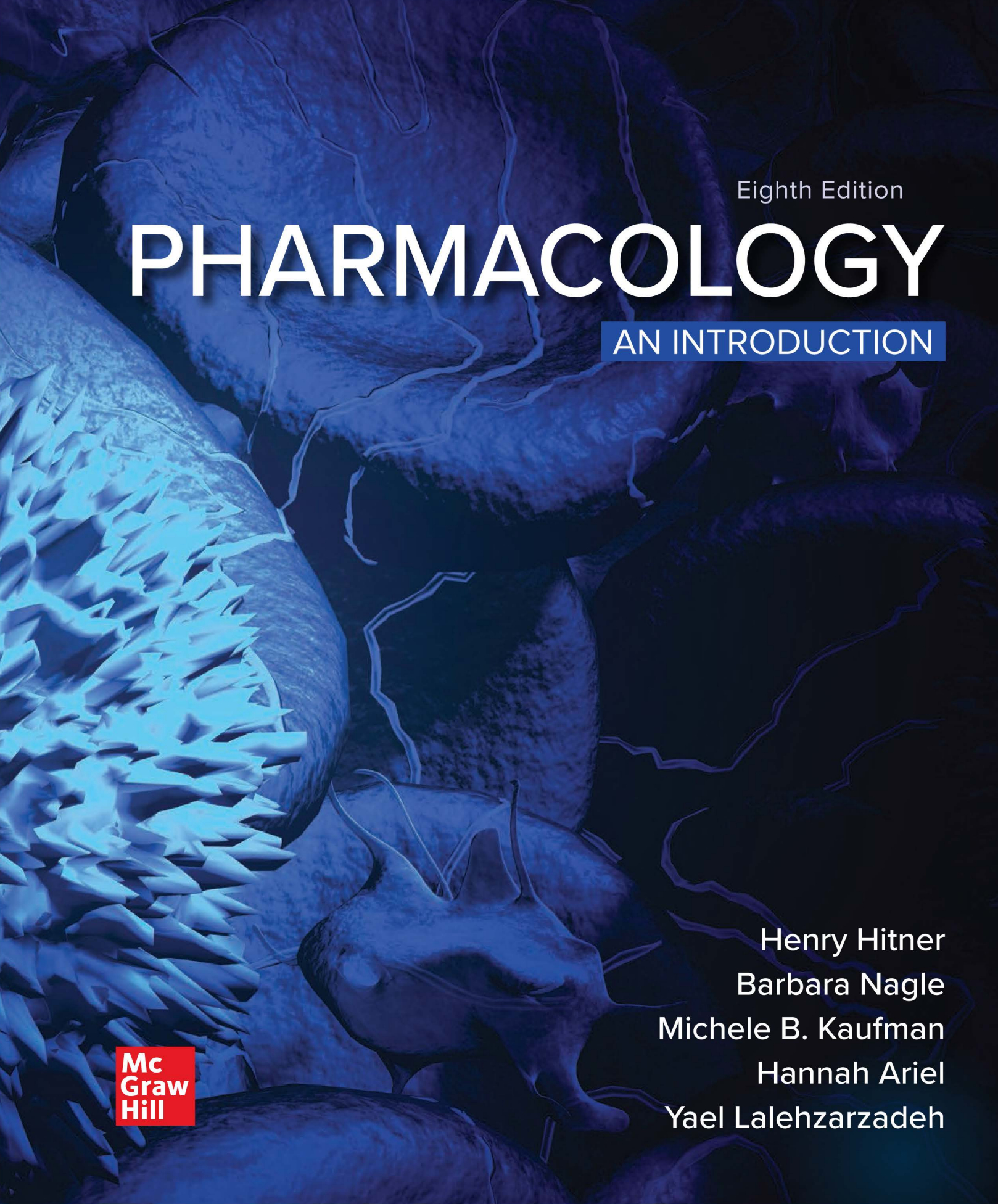
Eighth Edition
PHARMACOLOGY
AN INTRODUCTION
Henry Hitner
Barbara Nagle
Michele B. Kaufman
Hannah Ariel
Yael Lalehzarzadeh
Mc Graw Hill

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# Pharmacology

## An Introduction

8th edition


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PHARMACOLOGY



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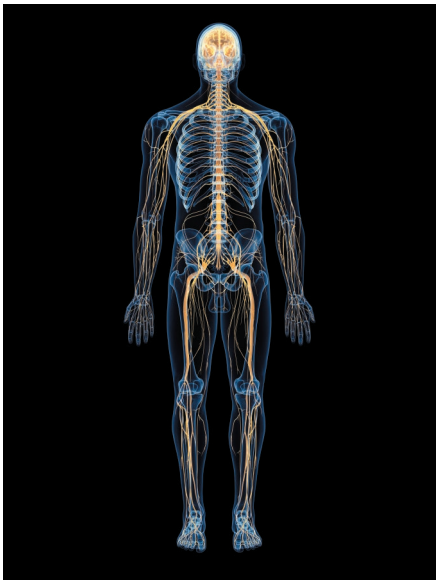

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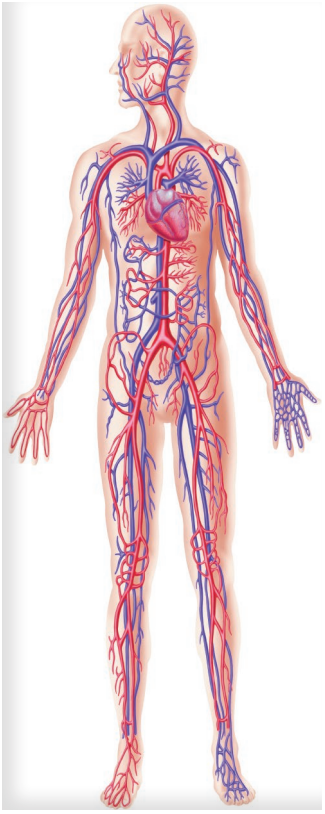

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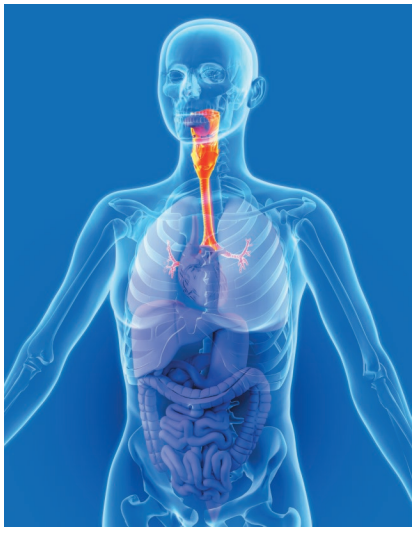

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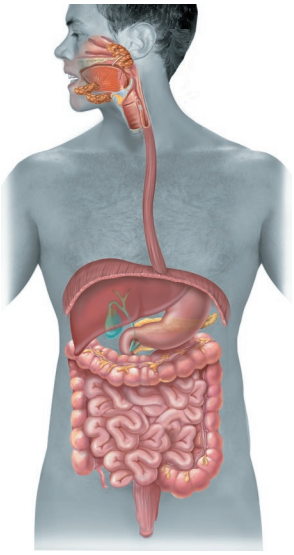

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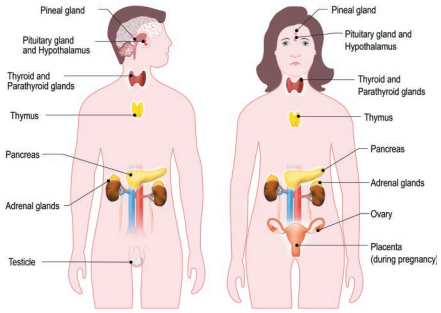


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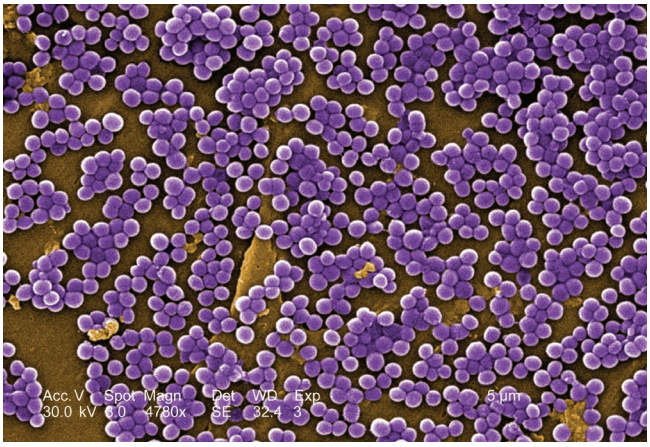


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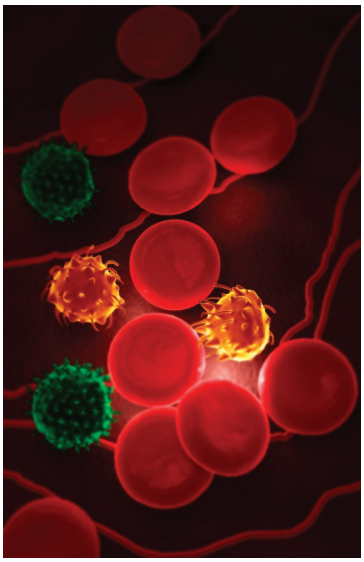

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# About the Authors

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**Henry Hitner** earned a bachelor of science degree in biology from Moravian College in Bethlehem, Pennsylvania, and spent several years working in the pharmaceutical industry, first as a research assistant in toxicology for Wyeth Laboratories and then as a research pharmacologist for National Drug Company, both in Philadelphia. During this time he earned a master of education degree in biology from West Chester University. He attended graduate school at Hahnemann Medical College in Philadelphia, where he earned a PhD in pharmacology. Dr. Hitner then went into academia, where he held numerous faculty positions, first as an instructor of biology and allied health sciences at Montgomery County Community College, followed by 30 years of teaching and research at the Philadelphia College of Osteopathic Medicine (PCOM). At PCOM he served as professor and vice chair of the neuroscience, physiology, and pharmacology department. Other positions included director of the animal facility and chair of the institutional animal care and utilization committee. Professional memberships included the Sigma Xi Scientific Research Society and the American Society for Pharmacology and Experimental Therapeutics. He was the recipient of the Lindback Foundation Award for Distinguished Teaching and a Mentor Award from the National Student Association. Henry and his wife Carlotta enjoy traveling, the beach, and time spent with family and their nine grandchildren.

**Barbara Nagle** earned a master of science and doctorate at Hahnemann Medical College and University in the department of pharmacology. Following postdoctoral training in ocular pharmacology at Will's Eye Hospital, Philadelphia, she taught pharmacology and physiology to medical students at the Philadelphia College of Osteopathic Medicine (PCOM) and to nursing students at Widener University. After several years in academia, she moved into the pharmaceutical industry at Glaxo Smith-Kline, Endo Pharmaceuticals, Bio-Pharm Clinical Services, ICON, and InKine Pharmaceuticals, Inc. as Director of Clinical Information and later Vice President of Clinical Research, Training and Quality Assurance. She has been part of the research effort to bring products through clinical development to FDA approval such as gastric acid suppressants (antihistamines), beta-blockers, antiinfectives, muscle relaxants, and oral contraceptives. Her most recent affiliation was with Endo Pharmaceuticals in pain management research prior to her current activities as consultant and educator. She has served as International Director of Drug Development Training and Medical Education for BioPharm. Professional memberships include the Sigma Xi Scientific Research and American Medical Writers Association. Barbara is a freelance photographer, traveler, and silk painter.

**Michele B. Kaufman,** a pharmacist at NewYork-Presbyterian Hospital Lower Manhattan is also a board-certified geriatric and registered pharmacist. She has over 30 years of pharmacy experience, and earned her bachelor of science in pharmacy from the University of Rhode Island (URI) College of Pharmacy, Kingston. She has worked as a product development pharmacist in New Jersey and as a hospital pharmacist at Robert Wood Johnson University Hospital in New Brunswick, before returning to New England (Boston) to obtain a doctor of pharmacy degree at Massachusetts College of Pharmacy/AHS.

(Boston) Subsequently, she completed a fellowship in drug information (DI) at the URI DI Center/RWMC in Providence. Dr. Kaufman then became a clinical assistant professor at St. John's University, Jamaica, New York, specializing in DI/adult medicine (clinical site @ LIJMC). After several years in academia she became a geriatric clinical pharmacist in corporate managed care, where she stayed for over a decade. She then left to pursue medical writing and health-system pharmacy practice. She is an active member of professional organizations, including American Society of Health-System Pharmacists, Academy of Managed Care Pharmacy, American Medical Writers Association, American Society of Consultant Pharmacists, New York State Council of Health-System Pharmacists, New York City Society of Health-System Pharmacists (NYCSHP), and SWINY. She is a member of the clinical care committee at Callen-Lorde Community Health Center (NYC). She has mentored numerous students throughout her years, and coauthored and published her first book (2019), a health careers book for middle-grade ages and up, *Healthcare Heroes: The Medical Careers Guide*. She is the past recipient of two prestigious awards from NYCSHP, the Harold Neham Award (2006) for dedication and commitment to pharmacy practice and literature; and the Joel Yellin Award (2011), honoring significant pharmacy practice contribution. When not working, Michele enjoys traveling, spending time with family and friends, exploring new cultures, and playing musical instruments, mostly the saxophone.

Hannah (Cooke) Ariel received her doctor of pharmacy degree from the University of Michigan, Ann Arbor. She was recruited by the Harvard Affiliated Hospital, Beth Israel Deaconess Medical Center, serving as a clinical pharmacist in cardiology and general medicine, with an adjunct appointment at Harvard Medical School as a clinical assistant professor, and a full-time pharmacy practice appointment as associate professor of pharmacy practice at Massachusetts College of Pharmacy in Boston. Hannah met and married Moshe Ariel of Brookline, and together they are raising their four children—Sarah, Aharon, Ariyeh, and Tova Anna—in Saddle Rock, Long Island, New York. Hannah has a great love for her family, in addition to her passion for science and medicine. Hannah is a licensed pharmacist in New York, Massachusetts, and Florida, and currently holds an adjunct faculty appointment in chemistry and biochemistry at Queens College, Queens, New York.

Yael Peimani-Lalehzarzadeh earned her doctor of pharmacy degree from The Arnold & Marie Schwartz College of Pharmacy and Health Sciences at Long Island University, Brooklyn, New York, where she graduated with honors. She was president of the American Society of Consultant Pharmacists (ASCP), LIU Brooklyn Chapter during the fall of 2014. Dr. Lalehzarzadeh has experience in both retail pharmacy and consulting for nursing homes. She is a devoted wife and mother, and cherishes every moment with her family.

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# Preface

The eighth edition of *Pharmacology: An Introduction* has been thoroughly updated, but the aim of this program remains what it has always been: to present a clear understanding of the basic concepts of pharmacology to the beginning student. Pharmacology is a complex subject that requires basic knowledge in many different scientific disciplines, particularly anatomy, physiology, and pathology. Health profession students often have limited exposure to these subjects, and one of the objectives of our text is to provide the necessary background information and to refresh the students' memory of previously learned material through which the therapeutic action of drugs can be clearly understood.

The goal of this text is to explain the **mechanisms of drug actions**. Understanding how drugs produce their effects allows the student to better understand the different pharmacologic actions and adverse effects that drugs produce. *Pharmacology: An Introduction* is designed for a variety of health profession programs requiring an understanding of pharmacology. The book presents a basic rationale for understanding current drug therapy. The drug information and chapter features are designed to be applicable and adaptable to many different educational programs. Personnel in the health and nursing professions spend much of their working time in direct contact with patients—observing, treating, and administering to the countless requirements and demands that constitute effective and responsible patient care. Therefore, it is important that students in health professions acquire a sound basic understanding of pharmacology as it relates to their particular needs.

New scientific discoveries and advances in the understanding of disease provide a continual introduction and approval of new drugs. At the same time, older drug therapies and drugs that cause serious adverse effects or other problems are eliminated. New advances in genetics and molecular biology have allowed the development of monoclonal antibodies and drugs with more selective mechanisms of action. These new agents can target specific receptors and physiologic functions that more accurately focus on the pathology of a particular disease process. Thus pharmacology is an ever-changing, growing body of knowledge that continually demands greater amounts of time and education from those in the health professions.

## Organization

*Pharmacology: An Introduction* is organized into **10 sections.** The introductory section, *General Concepts,* presents the basic concepts and pharmacologic principles that apply to all drugs. Subsequent sections present the drug classes that pertain to a specific body organ system (nervous, cardiovascular, respiratory, etc.) or therapeutic indication (antihypertensives, infectious diseases, antineoplastics, etc.). The discussion of each drug classification concentrates on the mechanisms of action, main therapeutic effects, clinical indications, adverse reactions, and drug interactions.

## Features

*Pharmacology: An Introduction's* hallmark features include:

- Readability: Short readable chapters that link theory to practice.
- Need-to-Know Information: The content is focused on need-to-know information, so not to overload the learner.
- Patient Administration and Monitoring Boxes: These features provide the student with critical patient information and patient instructions regarding the drugs discussed in the chapter.

**Other key features:**

- **Learning Outcomes** (LOs) have been completely revised in this edition. As always, the LOs are correlated to the Revised Bloom's Taxonomy and are numbered at the beginning of each chapter. LOs are linked to the main chapter topic headings, the end-of-chapter review questions, exam questions, instructor resources, and all content in Connect. This allows the student to more quickly associate the LOs with the location of that information in the text and with the answers to the review questions.
- ***Notes to the Health-Care Professional*** emphasize important points and information for medical personnel involved in drug administration.
- **Chapter reviews** at the end of each chapter progress from simple to complex and provide immediate reinforcement of terminology and pharmacologic concepts important for acquiring knowledge. The clinically relevant on-the-job questions allow students more opportunity to practice critical-thinking skills.

## What's New?

- Revision and numbering of all learning outcomes to reflect the Revised Bloom's Taxonomy guide the student on a clear path to mastering chapter content.

- Updated chapter names to more closely correlate with newer medical terminology.
- New drug classes listed for high cholesterol, blood pressure, migraine, heart failure, blood thinning, nausea and vomiting, osteoporosis, cancer, infectious diseases, autoimmune diseases, and Alzheimer's disease.
- Updated tables with new drugs, new drug classes, and removal of drugs no longer used.
- Updated table of new combination HIV drugs.
- Updated section on the opioid crisis and treatments for opioid use disorder (OUD).
- Updated sections on box warnings, risk evaluation and mitigation strategies (REMS), and information on cannabidiol (CBD).

Epocrates Rx Drugs, by Epocrates Medical Information 2020

- Correlation of learning outcomes to all major chapter headings and end-of-chapter review questions will help the student and instructor focus on key chapter content.
- Revised tables organize and summarize the main pharmacologic features of the different drug classes. **Most often the tables list the generic drug name first followed by the trade name(s), which are italicized and put within parentheses.** These drug tables are particularly useful for students in health information management programs.

Updated drug information has been found by using several key sources:

- US Federal Drug Administration (FDA) provides daily updates on drug approvals, drug safety issues, medication guides, and drug industry information.
- FDA database on drug approvals and discontinuations is used to check status of market availability of branded and generic drugs.
- *www.centerwatch.com* is a leading source of information about the clinical trials (pharmaceutical drugs and devices) industry since 1994.
- *www.factsandcomparisons.com* by Wolters Kluwer is a searchable database by drug name or therapeutic category for all FDA-approved drugs (by paid subscription).
- Lexicomp by Wolters Kluwer is a searchable drug information database (by paid subscription).
- National Library of Medicine and National Institutes of Health Medical provide information on conditions, diseases, wellness, over-the-counter (OTC) and prescription medication at different levels to facilitate understanding by professionals, students, patients, and consumers.
- WebMD Health Professional Network provides evidence-based content, updated regularly by more than 8000 attributed physician or health-care provider authors and editors, and the latest practice guidelines in 38 clinical areas.
- Aetna *InteliHealth* provides credible information from trusted sources, including Harvard Medical School and Columbia University College of Dental Medicine.
- Professional Organizations are dedicated to providing accurate information to patients and health-care providers on a specific disease or condition.

In addition to providing innovative approaches to learning pharmacology, McGraw Hill Education knows how much effort it takes to prepare for a new course. Through focus groups, symposia, reviews, and conversations with instructors like you, we have gathered information about the materials you need in order to facilitate successful courses. We are committed to providing you with high-quality, accurate instructor support.

## Additional Instructor Resources

- **Instructor's Manual** with course overview, lesson plans, answers for end-of-chapter exercises, competency correlations, Asset maps, and more.
- **PowerPoint Presentations** for each chapter, containing teaching notes correlated to learning outcomes. Each presentation seeks to reinforce key concepts and provide an additional visual aid for students.
- **Test Bank** and answer key for use in class assessment. The comprehensive test bank includes a variety of question types, with each question linked directly to a learning outcome from the text. Questions are also tagged with relevant topic, Bloom's Taxonomy level, difficulty level, and competencies. The test bank is available in Connect. Word and EZ Test versions are also available.

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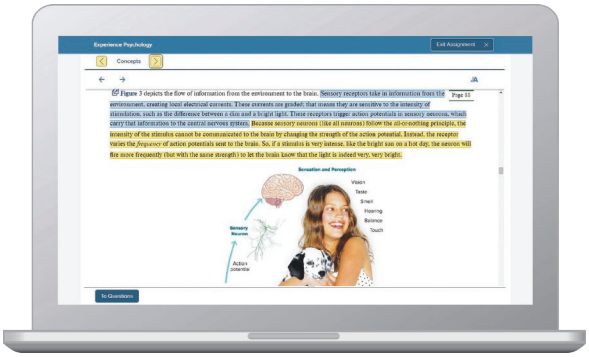

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> - Jordan Cunningham, Eastern Washington University


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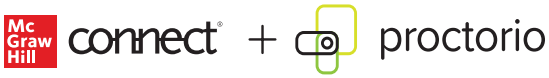
**Remote Proctoring & Browser-Locking Capabilities**




New remote proctoring and browser-locking capabilities, hosted by Proctorio within Connect, provide control of the assessment environment by enabling security options and verifying the identity of the student.

Seamlessly integrated within Connect, these services allow instructors to control students' assessment experience by restricting browser activity, recording students' activity, and verifying students are doing their own work.

Instant and detailed reporting gives instructors an at-a-glance view of potential academic integrity concerns, thereby avoiding personal bias and supporting evidence-based claims.

# Acknowledgments

A sincere thanks to our reviewers and contributors who helped shape the development of the eighth edition.

**Reviews**

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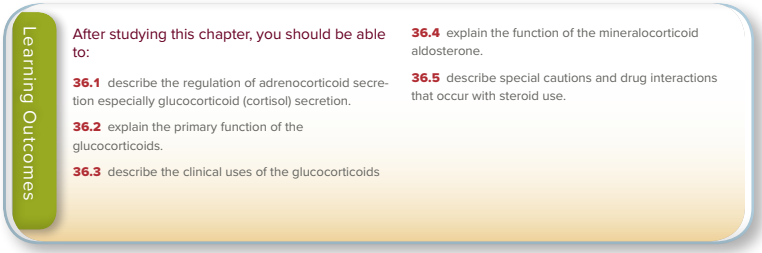
# What Every Student Needs to Know

**Many tools to help you learn have been integrated into *Pharmacology: An Introduction*.**

## Chapter Features

### Learning Outcomes

present the key points you should focus on when reading the chapter. Consider this your road map to the knowledge and skills you will acquire upon studying this content.


Learning Outcomes

After studying this chapter, you should be able to:

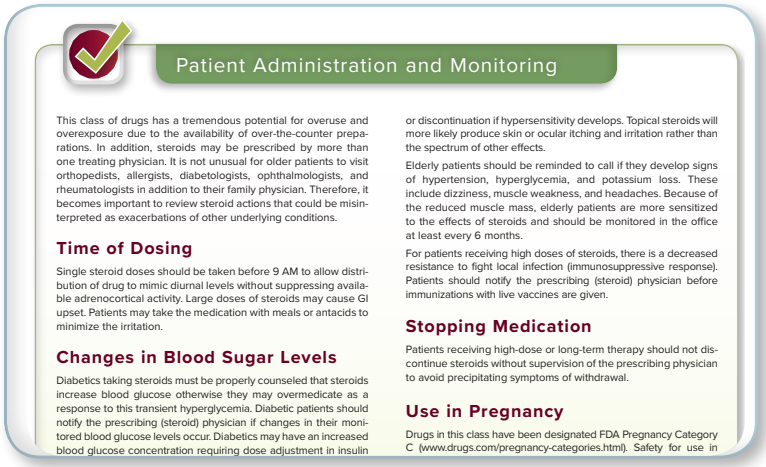
**36.1** describe the regulation of adrenocorticoid secretion especially glucocorticoid (cortisol) secretion.

**36.2** explain the primary function of the glucocorticoids.

**36.3** describe the clinical uses of the glucocorticoids

**36.4** explain the function of the mineralocorticoid aldosterone.

**36.5** describe special cautions and drug interactions that occur with steroid use.


Patient Administration and Monitoring

This class of drugs has a tremendous potential for overuse and overexposure due to the availability of over-the-counter preparations. In addition, steroids may be prescribed by more than one treating physician. It is not unusual for older patients to visit orthopedists, allergists, diabetologists, ophthalmologists, and rheumatologists in addition to their family physician. Therefore, it becomes important to review steroid actions that could be misinterpreted as exacerbations of other underlying conditions.

**Time of Dosing**

Single steroid doses should be taken before 9 AM to allow distribution of drug to mimic diurnal levels without suppressing available adrenocortical activity. Large doses of steroids may cause GI upset. Patients may take the medication with meals or antacids to minimize the irritation.

**Changes in Blood Sugar Levels**

Diabetics taking steroids must be properly counseled that steroids increase blood glucose otherwise they may overmedicate as a response to this transient hyperglycemia. Diabetic patients should notify the prescribing (steroid) physician if changes in their monitored blood glucose levels occur. Diabetics may have an increased blood glucose concentration requiring dose adjustment in insulin or discontinuation if hypersensitivity develops. Topical steroids will more likely produce skin or ocular itching and irritation rather than the spectrum of other effects.

Elderly patients should be reminded to call if they develop signs of hypertension, hyperglycemia, and potassium loss. These include dizziness, muscle weakness, and headaches. Because of the reduced muscle mass, elderly patients are more sensitized to the effects of steroids and should be monitored in the office at least every 6 months.

For patients receiving high doses of steroids, there is a decreased resistance to fight local infection (immunosuppressive response). Patients should notify the prescribing (steroid) physician before immunizations with live vaccines are given.

**Stopping Medication**

Patients receiving high-dose or long-term therapy should not discontinue steroids without supervision of the prescribing physician to avoid precipitating symptoms of withdrawal.

**Use in Pregnancy**

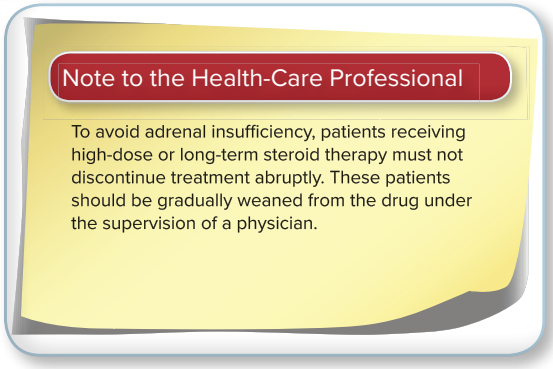
Drugs in this class have been designated FDA Pregnancy Category C (www.drugs.com/pregnancy-categories.html). Safety for use in

### *Patient Administration and Monitoring boxes*

summarize important patient information and patient instructions about the drugs discussed in that chapter. It will expand your knowledge of medications and conditions.

### *Notes to the Health-Care Professional*

emphasizes important points and information for medical personnel involved in drug administration.


Note to the Health-Care Professional

To avoid adrenal insufficiency, patients receiving high-dose or long-term steroid therapy must not discontinue treatment abruptly. These patients should be gradually weaned from the drug under the supervision of a physician.

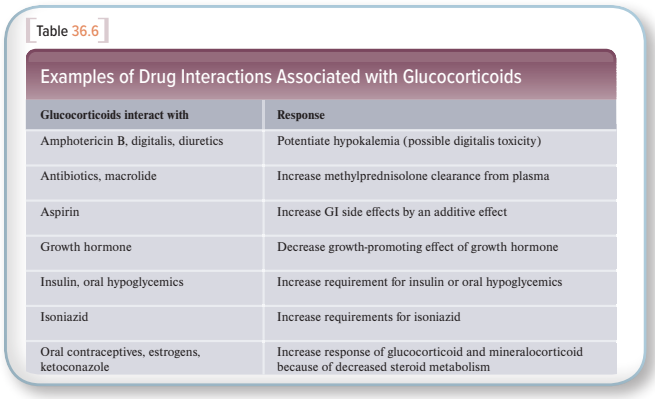


Table 36.6

Examples of Drug Interactions Associated with Glucocorticoids

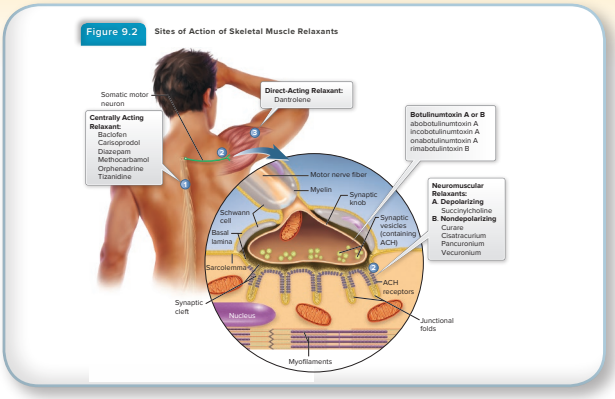
| Glucocorticoids interact with | Response |
|---|---|
| Amphotericin B, digitalis, diuretics | Potentiate hypokalemia (possible digitalis toxicity) |
| Antibiotics, macrolide | Increase methylprednisolone clearance from plasma |
| Aspirin | Increase GI side effects by an additive effect |
| Growth hormone | Decrease growth-promoting effect of growth hormone |
| Insulin, oral hypoglycemics | Increase requirement for insulin or oral hypoglycemics |
| Isoniazid | Increase requirements for isoniazid |
| Oral contraceptives, estrogens, ketoconazole | Increase response of glucocorticoid and mineralocorticoid because of decreased steroid metabolism |

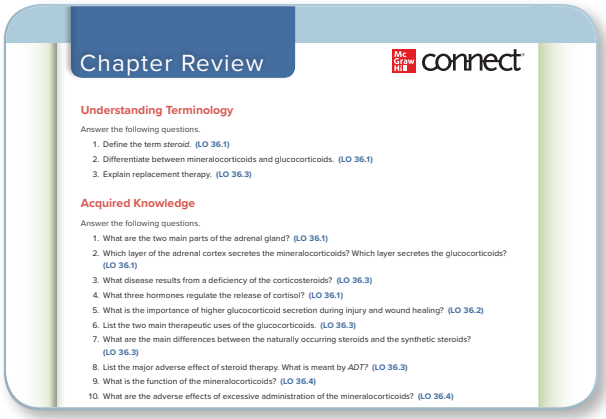
### Drug Tables

organize and summarize the main pharmacologic features of the different drug classes. The tables most often list the generic drug name first followed by the trade name(s), which are italicized and put within parentheses.

## Illustrations and Photos

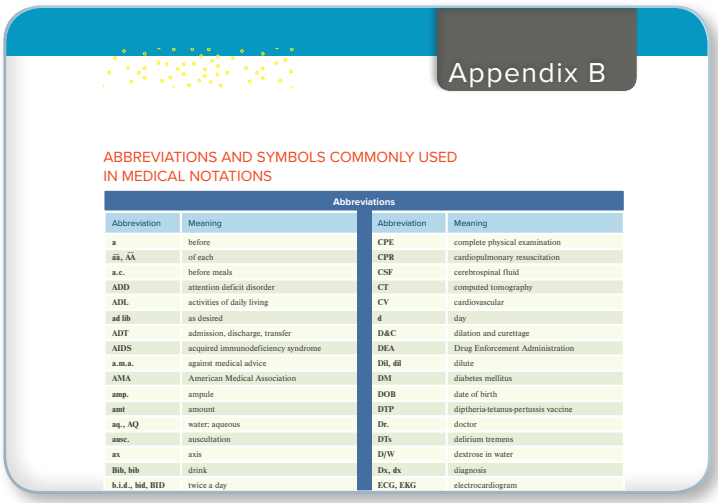
provide a dynamic visual picture of the action of drugs and drug products to help you understand pharmacologic processes that are discussed in the text. Illustrations provide just the right level of detail to help explain the processes described.




## Chapter Reviews

provide immediate reinforcement of terminology and pharmacological concepts important for acquiring knowledge. These questions, which are also available in Connect, challenge you to apply information presented in the chapter. The clinically relevant on-the-job questions allow you more opportunity to practice critical-thinking skills.




## Appendices

provide additional information pertinent to the study of pharmacology. You will find lists of abbreviations and symbols used in medical notations, weights and measures, and mathematical functions and terms.

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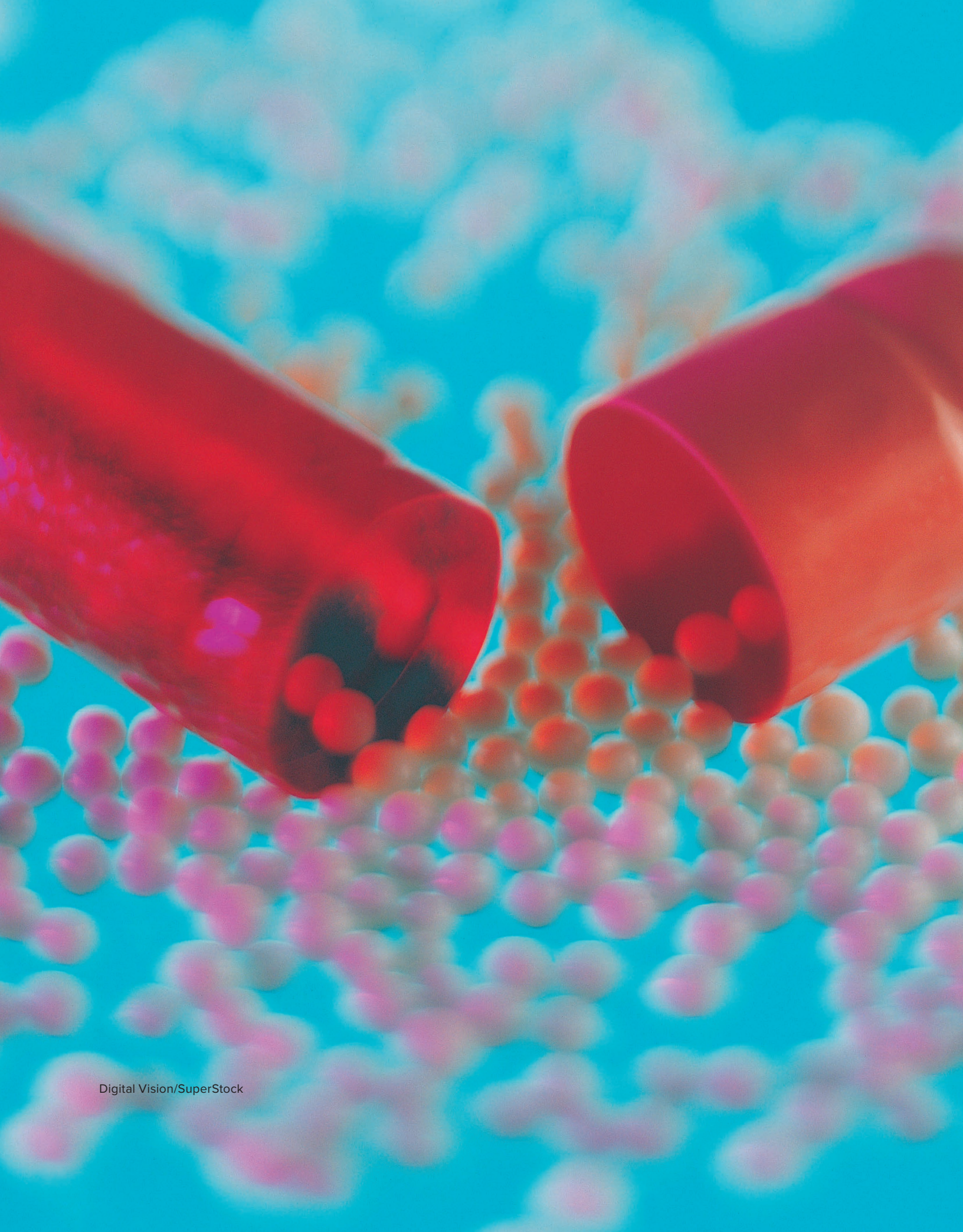

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PART 1

# General Concepts



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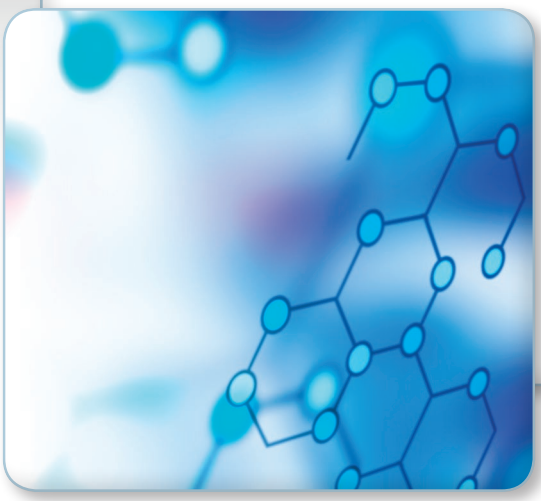
Chapter 1



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# Pharmacology: An Introduction

## KEY TERMS

**adverse effect:** general term for undesirable and potentially harmful drug effect.

**agonist:** drug that binds to a receptor and activates a physiologic response or drug action.

**antagonist:** drug that binds to a receptor and interferes with other drugs or substances from producing a drug effect.

**chemical name:** name that defines the chemical composition of a drug.

**contraindications:** situations or conditions when a certain drug should not be administered.

**controlled substance:** drug that has the potential for abuse and thus is regulated by law.

**dose:** a measurement of the amount of drug that is administered.

**drug:** chemical substance that produces a change in body function.

**drug indications:** intended or indicated uses for any drug.

**ED50:** effective dose 50, or dose that will produce an effect that is half of the maximal response.

**generic name:** nonproprietary name of a drug.

**LD50:** lethal dose 50, or dose that will kill 50 percent of the laboratory animals tested.

**mechanism of action:** explanation of how a drug produces its effects.

**nonprescription, over-the-counter (OTC) drug:** drug that can be purchased without the services of a physician.

**pharmacology:** study of drugs.

**potency:** measure of the strength, or concentration, of a drug required to produce a specific effect.

**prescription drug:** drug for which dispensing requires a written or phone order that can only be issued by or under the direction of a licensed physician.

**receptor:** specific cellular structure that a drug binds to in order to produce a physiologic effect.

**side effect:** drug effect other than the therapeutic effect that is usually undesirable but not harmful.

**site of action:** location within the body where a drug exerts its therapeutic effect, often a specific drug receptor.

**therapeutic effect:** desired drug effect to alleviate some condition or symptom of disease.

**therapeutic index (TI):** ratio of the LD50 to the ED50 in animal studies.

**toxic effect:** undesirable drug effect that implies drug poisoning; can be very harmful or life-threatening.

**trade name:** patented proprietary name of a drug sold by a specific drug manufacturer; also referred to as the brand name.

## Learning Outcomes

After studying this chapter, you should be able to:

**1.1** list and define the major areas of pharmacology.

**1.2** describe what a drug is and explain the differences between therapeutic effect, side effect, and toxic effect.

**1.3** understand the terms **site of action** and **mechanism of action**, and how agonist and antagonist drugs interact at drug receptor sites.

**1.4** characterize the relationship between drug dosage and drug response, and the relationship between drug response and time.

**1.5** understand the terms associated with drug safety: *therapeutic index, idiosyncrasy, drug allergy,* and *teratogen*.

**1.6** explain the nomenclature used to name and classify drugs.

**1.7** recall the main drug references and the information they provide.

## Introduction

**Pharmacology** is the study of drugs. A drug can be any substance that, when administered to living organisms, produces a change in function. Thus, substances such as water, metals (iron), or insecticides can be classified as drugs. However, the term *drug* commonly refers to any medication that is used for diagnosing, curing, or treating disease.

Pharmacology is a subject that requires some background knowledge of anatomy, physiology, pathology, and related medical sciences. In that sense pharmacology is an integrative course of study that applies the relevant information of all medical sciences to the treatment of disease. Throughout this textbook the essential background information of anatomy, physiology, and pathology required for an understanding of drug action will be reviewed. The major focus of *Pharmacology: An Introduction* is to provide an understanding of the mechanisms of action, main therapeutic effects, clinical uses, and adverse reactions of drugs. Completion of an introductory pharmacology course is only the beginning step in understanding this complex subject.

LO 1.1

# DRUG SOURCES AND MAJOR AREAS OF PHARMACOLOGY

## Drug Sources

A logical question to ask about pharmacology is, "Where do drugs come from?" There are several sources of drugs. In the early days of medicine, most drugs were obtained from plant or animal sources. Plants and living organisms contain active substances that can be isolated, purified, and formulated into effective drug preparations. Examples of drugs derived from plants that are still widely used today include the analgesics morphine and codeine, which were obtained from the poppy plant (*Papver somniferum*); the heart drug digitalis, which was obtained from the purple foxglove (*Digitalis purpurea*); and the antimalarial drug quinine, which was obtained from the bark of the cinchona tree. Paclitaxel, an anticancer drug, is obtained from the yew tree. The search for new plant drugs is still very active. It is also interesting that many of the drugs of abuse such as cocaine, marijuana, mescaline, heroin, and others are derived from plants. Most of these drugs were used for hundreds of years by many different cultures in their religious and ritual ceremonies. Drugs obtained from living organisms include hormones such as insulin (from the pig) and growth hormone from pituitary glands. In addition, antibiotics such as cephalosporins and aminoglycosides have been derived from bacteria. The early history of pharmacology is filled with many interesting stories of discovery and medical experimentation. Textbooks devoted to the history of medicine and pharmacology are the best sources for additional information. Despite the many examples of drugs obtained from plants and living organisms, the main

Table 1.1

**Major Areas of Pharmacology**

| Area | Description |
|---|---|
| Pharmacodynamics | Study of the action of drugs on living tissue |
| Pharmacokinetics | Study of the processes of drug absorption, distribution, metabolism, and excretion |
| Pharmacotherapeutics | Study of the use of drugs in treating disease |
| Pharmacy | Science of preparing and dispensing medicines |
| Posology | Study of the amount of drug that is required to produce therapeutic effects |
| Toxicology | Study of the harmful effects of drugs on living tissue |

source of new drugs today is from chemical synthesis. Also, many of the drugs that once were obtained from plants and animals are now chemically synthesized in pharmaceutical laboratories. Advances in molecular biology and gene therapy have generated new types of drugs such as monoclonal antibodies.

Pharmacology is a large discipline that can be subdivided into different areas of study. These include pharmacodynamics, pharmacokinetics, pharmacotherapeutics, pharmacy, posology, and toxicology. These areas of study are described in Table 1.1.

LO 1.2

## TERMINOLOGY RELATED TO DRUG EFFECTS

### Major Areas of Pharmacology

Another basic question that should be answered is, "What actually is a **drug**?" Every pure drug is a chemical compound with a specific chemical structure. Because of its structure, a drug has certain properties that are usually divided into chemical properties and biological properties. The properties of any drug determine what effects will be produced when the drug is administered. An important fact to remember is that, structurally, the human body is composed mostly of cells, even though these cells are highly organized into tissues, organs, and systems. Consequently, drugs produce effects by influencing the function of cells.

Pharmacologists know that all drugs produce more than one effect. Every drug produces its intended effect, or **therapeutic effect**, along with other effects. The therapeutic use(s) of any drug is referred to as the **drug indication**, meaning indications for use. The term **contraindication** refers to the situation or circumstance when a particular drug should *not* be used. Some drug effects, other than therapeutic effects, are described as undesirable. Undesired drug effects are categorized as side effects, adverse effects, and toxic effects.

### Side Effects

Many **side effects** are more of a nuisance than they are harmful. The dry mouth and sedation caused by some antihistamine drugs is an example. In many cases drug side effects must be tolerated to benefit from the therapeutic actions of the drug.

### Adverse Effects

**Adverse effects** are also undesired effects, but these are effects that may be harmful (persistent diarrhea, vomiting, or central nervous system [CNS] disturbances such as confusion) or that with prolonged treatment may cause conditions that affect the function of vital organs such as the liver or kidney. Reduction of dosage or switching to an alternative drug often will avoid or minimize these harmful consequences.

### Toxic Effects

**Toxic effects**, or toxicity, implies drug poisoning, the consequences of which can be extremely harmful and may be life-threatening. In these situations, the drug must be stopped and supportive treatment and the administration of antidotes may be required.

The term most frequently used to describe the undesirable effects of drugs is *adverse effects.* However, you should be familiar with the other terms because they are used and, if used correctly, describe the nature and potential severity of undesired drug effects.

Most drugs will cause all three types of undesired effects, depending on the dose administered. At low doses, side effects are common and often expected. At higher doses, additional adverse effects may appear. At very high doses, toxic effects may occur that can be fatal. Consequently, the undesired effects produced by most drugs are often a function of dosage, which is why a well-known physician from the Middle Ages, Paracelsus (1493–1541), made the famous statement, "Only the dose separates a drug from a poison"—and we could add, "a therapeutic effect from a toxic effect." Allied health personnel spend the majority of their time in patient contact. Therefore, they have an important responsibility to observe the undesired effects of drugs, to recognize the side effects that are often expected, and to identify and report the adverse and toxic effects that are potentially harmful and that often require medical attention.

LO 1.3

## BASIC CONCEPTS IN PHARMACOLOGY

As in any subject, fundamental principles and concepts form the basis upon which additional information can be added. Pharmacology is no exception, and the following basic concepts apply to any drug.

### Site of Action

The **site of action** of a drug is the location within the body where the drug exerts its therapeutic effect. The site of action of some drugs is not known; however, the site of action for most drugs has been determined. For example, the site of action of aspirin to reduce fever is in an area of the brain known as the hypothalamus. Within the hypothalamus the temperature-regulating center controls and maintains body temperature. Aspirin alters the activity of the hypothalamus so that body temperature is reduced. Throughout this book, when the site of drug action is known or suspected, it will be presented.

### Mechanism of Action

**Mechanism of action** explains how a drug produces its effects. For example, local anesthetic agents produce a loss of pain sensation by interrupting nerve conduction in sensory nerves. For nerve impulses to be conducted, sodium ions must pass through the nerve membrane. Local anesthetic agents attach to the nerve membrane and prevent the passage of sodium ions. Consequently, sensory nerve impulses for pain are not conducted to the pain centers in the brain. Knowledge of the mechanism of action of drugs is essential to understanding why drugs produce the effects that they do.

### Receptor Site

Drug action is usually thought to begin after a drug has attached itself to some chemical structure located on the outer cell membrane or within the cell itself. For a few drugs and for some normal body substances, there seems to be a specific location on certain cells. This area is referred to as the **receptor** site. The attachment, or binding, of a drug to its receptors begins a series of cell changes referred to as the drug action.

When a specific receptor site for a drug is known, that receptor site becomes the site of action for that particular drug. Morphine, an analgesic drug, is an example of a drug that binds to a specific receptor. The receptors for morphine are located in the brain and are known as the morphine, or opioid, receptors. When morphine binds to its receptors, it produces cell changes that reduce the perception of pain. There are many different pharmacologic receptors, and they will be described in the appropriate chapters.

### Agonists and Antagonists

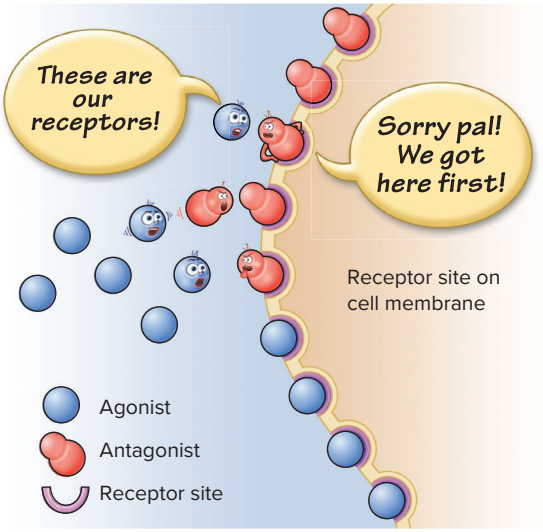
Drugs that bind to specific receptors and produce a drug action are called **agonists**. Morphine is an example of an agonist. Drugs that bind to specific receptors and block agonist drug action or cellular functions are called **antagonists**.

Antagonists are also known as blocking drugs. Usually, antagonists bind to a specific receptor to displace or prevent an agonist drug or body substance from activating that receptor. Naloxone, a morphine antagonist, is administered to prevent, or antagonize, the effects of morphine in cases of morphine overdose. There are many examples in pharmacology where drug antagonists are used to prevent other substances from exerting an effect.

When both agonist and antagonist drugs bind to the same receptor and are administered together, they compete with each other for the same receptor site. This effect is known as *competitive antagonism.* The amount of drug action produced depends on which drug (agonist or antagonist) occupies the greatest number of receptors. The actions of a drug agonist and antagonist are illustrated in Figure 1.1. There is also uncompetitive antagonism, which occurs when the antagonist drug interferes with the agonist drug action but not by binding to the same receptor.

Figure 1.1

**Competitive Antagonism at Work**




LO 1.4

## DOSE-RESPONSE AND TIME-PLASMA DRUG CONCENTRATION CURVES

### Dose-Response Curve

A fundamental principle of pharmacology is that the response to any drug depends on the amount of drug given. This principle is known as the dose-response relationship. A **dose** is the exact amount of a drug that is administered to produce a specific effect. The effect is referred to as the response. When the relationship between the dose and the response is plotted as a graph, it is referred to as a dose-response curve.

Figure 1.2 illustrates the appearance of a typical dose-response curve for two similar drugs. The main feature of the dose-response relationship is that a drug response is proportional to the dose. As the dose increases, so does the magnitude of the response. Eventually, a *maximal response* is usually attained (100 percent response); further increases in dose do not produce any greater effect. This point on the graph is known as the ceiling effect. The *ceiling effect* reflects the limit of some drug classes to produce a particular effect. Above a certain dosage no further increase in effect is observed. Doses above those needed to produce the ceiling effect usually cause other undesired, often toxic, drug effects. Drugs within a drug class that are more potent than other drugs in the same class will produce the ceiling effect at a lower dosage, but they will not "raise the ceiling." Drugs that continue to cause an increased effect as long as the dose is increased do not have a ceiling effect.

A graded dose-response curve can be used to evaluate drug response among different drugs. In a graded dose-response curve, the increases in drug dosage are plotted against the increases in drug response. For example, dose-response curves are used to compare the potency of similar drugs. **Potency** is a measure of the strength, or concentration, of a drug required to produce a specific effect. The dose that will produce an effect that is half of the maximal response is referred to as the effective dose 50, or **ED50**.

The ED50 can be used to compare the potency of drugs that produce the same response. In Figure 1.2, the ED50 of drug A is 10 mg while the ED50 of drug B is 20 mg. Therefore, drug A is twice as potent as drug B. Twice the concentration of drug B is needed to produce the same response as drug A.

Quantal (referred to as all-or-none) dose-response curves are used to show the percentage of a human or animal population that responds to a specific drug dosage. This information is important for determining the dosages that are recommended for various treatments. Quantal dose-response curves require an understanding of mathematical statistics that is beyond the scope of this textbook.

### Time-Plasma Drug Concentration Curve

The relationship of time and the plasma drug concentration is known as the time-plasma drug concentration curve or time-response curve since it reflects the

Figure 1.2

**A Typical Dose-Response Curve**

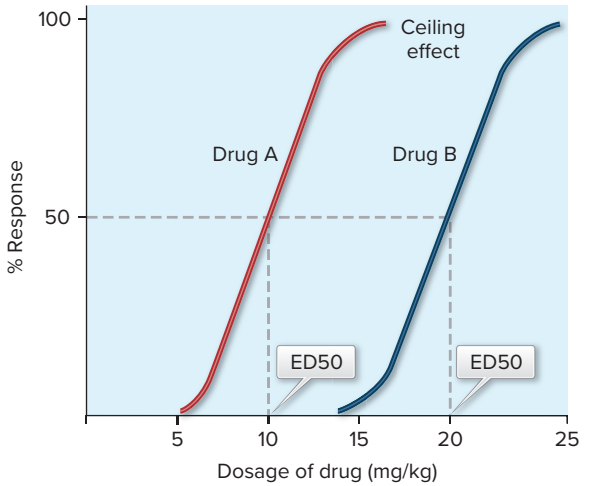
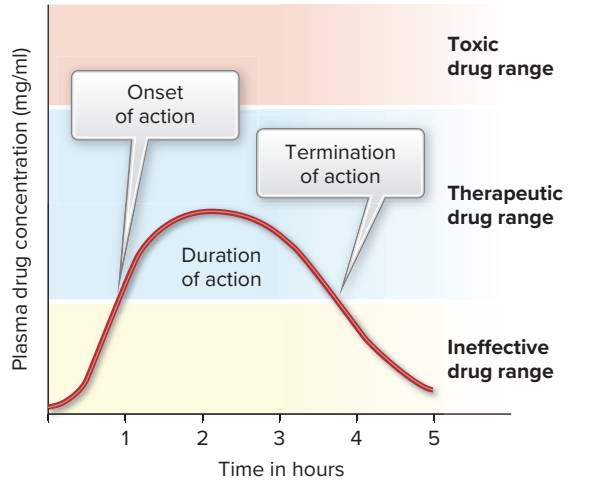


Figure 1.3

**A Typical Time-Plasma Drug Concentration Curve**




**This curve shows the change in plasma drug concentration over time in relation to onset, duration, and termination of drug action. Plasma drug concentrations that exceed the therapeutic range produce drug toxicity.**

duration of action. *Duration of action* is the length of time that a drug continues to produce its effect. Most individual drugs produce effects over a relatively constant period of time. Figure 1.3 illustrates the appearance of a typical time-plasma drug concentration curve. In this example, the plasma drug concentration is correlated with the onset, duration, and termination of drug action. After drug administration, a certain amount of time is required before a drug will produce an observable effect. The time from drug administration to the first observable effect is known as the *onset of action.* The drug response will continue as long as there is an effective concentration of the drug at the site of action. As the drug is metabolized and excreted, the response gradually decreases because the drug level is decreasing. When the plasma drug concentration falls below the therapeutic range, there is *termination of drug action.* Time-plasma drug concentration curves are used for predicting the frequency with which a drug must be administered in order to maintain an effective drug response.

LO 1.5

## DRUG SAFETY

The federal Food and Drug Administration (FDA) has established guidelines that govern the approval and use of all drugs. Every drug must fulfill two major requirements before it can be approved for use in humans: efficacy (proof of effectiveness) and safety. The drug must be effective in the disease state for which it has been approved. Approved drugs must satisfy specific safety criteria as determined by extensive animal testing and controlled human testing. As discussed previously, the dose separates therapeutic effects from toxic effects.

### Note to the Health-Care Professional

All drugs will act as poisons if taken in excess. Only the dose separates a therapeutic effect from a toxic effect. The goal of drug therapy is to select a dose that is in the therapeutic range and avoid doses that produce toxicity. This task is not easy because many factors influence the amount of drug that reaches its site of action. These factors—such as route of administration, absorption, and drug metabolism—will be discussed in Chapter 2.

Drug safety receives much attention today. It is a constant source of concern and debate because the public is more aware of the dangers of drugs. To receive approval for use in humans, a drug must undergo several years of both animal and human testing and evaluation. Several animal species must be used to evaluate the effectiveness and toxicity of a drug. One of the first tests that is performed is the lethal dose 50, or **LD50**. The LD50 is the dose that will kill 50 percent of the animals tested. The results of the LD50 and other tests are used to predict the safety of a drug.

### Therapeutic Index

The **therapeutic index (TI)** is a ratio of the LD50 to the ED50 of a drug. It gives an estimate of the relative safety of a drug. The equation is expressed as:

$$TI = LD50/ED50 = 1000 \text{ mg}/100 \text{ mg} = 10$$

In this example, the therapeutic index is 10. This index indicates that 10 times as much drug is needed to produce a lethal effect in 50 percent of the animals as is needed to produce the therapeutic effect in 50 percent of the animals. The therapeutic index is used only in animal studies to establish dosage levels for other testing procedures. The goal of drug therapy is to achieve therapeutic effects in all individuals without producing any harmful effects.