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LAURA D. ROSENTHAL

Lehne's PHARMACOLOGY for Nursing Care

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Lehne's PHARMACOLOGY for Nursing Care

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ELEVENTH EDITION

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To those health care workers who have risked their lives
in the ongoing fight against the COVID-19 virus.
LDR and ***JRB***

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Her favorite activities involve spending time with family. She also enjoys working on the family hobby farm and cutting fabric into small pieces that she sews back together.

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Preface

Pharmacology pervades all phases of nursing practice and relates directly to patient care and education. Yet despite its importance, many students—and even some teachers—are often uncomfortable with the subject. Why? Because traditional texts have stressed *memorizing* rather than *understanding*. In this text, the guiding principle is to establish a basic understanding of drugs, after which secondary details can be learned as needed.

This text has two major objectives: (1) to help you, the nursing student, establish a knowledge base in the basic science of drugs and (2) to show you how that knowledge can be applied in clinical practice. The methods by which these goals are achieved are described in the following sections.

LAYING FOUNDATIONS IN BASIC PRINCIPLES

To understand drugs, you need a solid foundation in basic pharmacologic principles. To help you establish that foundation, this text has major chapters on the following topics: basic principles that apply to all drugs (Chapters 4 through 10), basic principles of drug therapy across the life span (Chapters 11 through 13), basic principles of neuropharmacology (Chapter 14), basic principles of antimicrobial therapy (Chapter 87), and basic principles of cancer chemotherapy (Chapter 105).

REVIEWING PHYSIOLOGY AND PATHOPHYSIOLOGY

To understand the actions of a drug, it is useful to understand the biologic systems influenced by the drug. Accordingly, for all major drug families, relevant physiology and pathophysiology are reviewed. In almost all cases, these reviews are presented at the beginning of each chapter rather than in a systems review at the beginning of a unit. This juxtaposition of pharmacology, physiology, and pathophysiology is designed to help you understand how these topics interrelate.

TEACHING THROUGH PROTOTYPES

Within each drug family we can usually identify a prototype—a drug that embodies the characteristics shared by all members of the group. Because other family members are similar to the prototype, to know the prototype is to know the basic properties of all family members.

The benefits of teaching through prototypes can be appreciated with an example. Let's consider the nonsteroidal anti-inflammatory drugs (NSAIDs), a family that includes aspirin, ibuprofen [Motrin], naproxen [Aleve], celecoxib [Celebrex], and more than 20 other drugs. Traditionally, information on these drugs is presented in a series of paragraphs describing each drug in turn. When attempting to study from such a list, you are likely to learn many drug names and little else; the important concept of similarity among family members is easily lost. In this text, the family prototype—aspirin—is discussed first and in depth. After this, the small ways in which individual NSAIDs differ from aspirin are pointed out. Not only is this approach more efficient than the traditional approach, it is also more effective in that similarities among family members are emphasized.

LARGE PRINT AND SMALL PRINT: A WAY TO FOCUS ON ESSENTIALS

Pharmacology is exceptionally rich in detail. There are many drug families, each with multiple members and each member with its own catalog of indications, contraindications, adverse effects, and drug interactions. This abundance of detail confronts teachers with the difficult question of what to teach and confronts students with the equally difficult question of what to study. Attempting to answer these questions can frustrate teachers and students alike. Even worse, basic concepts can be obscured in the presence of myriad details.

To help you focus on essentials, two sizes of type are used in this text. Large type is intended to say, "On your first exposure to this topic, this is the core of information you should learn." Small type is intended to say, "Here is additional information that you may want to learn after mastering the material in large type." As a rule, we reserve large print for prototypes, basic principles of pharmacology, and reviews of physiology and pathophysiology. We use small print for secondary information about the prototypes and for the discussion of drugs that are not prototypes. This technique allows the book to contain a large body of detail without having that detail cloud the big picture. Furthermore, because the technique highlights essentials, it minimizes questions about what to teach and what to study.

The use of large and small print is especially valuable for discussing adverse effects and drug interactions. Most drugs are associated with many adverse effects and interactions. As a rule, however, only a few of these are noteworthy. In traditional texts, practically all adverse effects and interactions are presented, creating long and tedious lists. In this text, we use large print to highlight the few adverse effects and interactions that are especially characteristic; the rest are noted briefly in small print. Rather than overwhelming you with long and forbidding lists, this text delineates a moderate body of information that is truly important, thereby facilitating comprehension.

USING CLINICAL REALITY TO PRIORITIZE CONTENT

This book contains two broad categories of information: pharmacology (the basic science about drugs) and therapeutics (the clinical use of drugs). To ensure that content is clinically relevant, we use evidence-based treatment guidelines as a basis for deciding what to stress and what to play down. Unfortunately, clinical practice is a moving target.

Guidelines change when effective new drugs are introduced and when clinical trials reveal new benefits or new risks of older drugs, and so we need to work hard to keep this book current. Despite our best efforts, the book and clinical reality may not always agree: Some treatments discussed here will be considered inappropriate before the 12th edition is published. Furthermore, in areas where controversy exists, the treatments discussed here may be considered inappropriate by some clinicians right now.

NURSING IMPLICATIONS: DEMONSTRATING THE APPLICATION OF PHARMACOLOGY IN NURSING PRACTICE

The principal reason for asking you to learn pharmacology is to enhance your ability to provide patient care and education. To show you how pharmacologic knowledge can be applied to nursing practice, nursing implications are integrated into the body of each chapter. That is, as specific drugs and drug families are discussed, the nursing implications inherent in the pharmacologic information are noted side by side with the basic science.

To facilitate access to nursing content, nursing implications are also summarized at the end of most chapters. These summaries serve to reinforce the information presented in the chapter body. These summaries have been omitted in chapters that are especially brief or that address drugs that are infrequently used. Even in these chapters, however, nursing implications are incorporated into the main chapter text.

In addition, "Safety Alert" features throughout draw attention to important safety concerns related to contraindications, adverse effects, pregnancy categories, and more.

WHAT'S NEW IN THE BOOK?

Lehne's Pharmacology for Nursing Care has been revised cover to cover to ensure that the latest and most accurate information is presented. Three new chapters help promote our focus on the most useful and most critical information for nursing students:

- Genetic and Genomic Considerations
- Introduction to Immunomodulators
- Muscarinic Antagonists

In addition, **thoroughly updated drug content** reflects the latest U.S. Food and Drug Administration (FDA) drug approvals, withdrawals, and therapeutic uses with revisions to the corresponding nursing content.

LEARNING SUPPLEMENTS FOR STUDENTS

- Online Evolve Resources accompany this edition and include **Downloadable Key Points, Review Questions, Unfolding Case Studies**, and more. These resources are available at http://evolve.elsevier.com/Lehne.
- **Pharmacology Online** for *Lehne's Pharmacology for Nursing Care*, 11th edition, is a dynamic online course resource that includes interactive self-study modules, a collection of interactive learning resources, and a media-rich library of supplemental resources.
- The ***Study Guide***, which is keyed to the book, includes study questions; critical thinking, prioritization, and delegation questions; and case studies.

TEACHING SUPPLEMENTS FOR INSTRUCTORS

- The Instructor Resources for the 11th edition are available online and include Next-Generation NCLEX® Examination-Style Questions, TEACH® for Nurses Lesson Plans, a Test Bank, a PowerPoint Collection, and an Image Collection.

WAYS TO USE THIS TEXTBOOK

Thanks to its focus on essentials, this text is especially well suited to serve as the primary text for a course dedicated specifically to pharmacology. In addition, the focused approach makes it a valuable resource for pharmacologic instruction within an integrated curriculum and for self-directed learning by students, teachers, and practitioners.

How is this focus achieved? Four primary techniques are employed: (1) teaching through prototypes, (2) using standard print for essential information and small print for secondary information, (3) limiting discussion of adverse effects and drug interactions to information that matters most, and (4) using evidence-based clinical guidelines to determine what content to stress. To reinforce the relationship between pharmacologic knowledge and nursing practice, nursing implications are integrated into each chapter. To provide rapid access to nursing content, nursing implications are summarized at the end of most chapters using a nursing process format. In addition, key points are listed at the end of each chapter. As in previous editions, the 11th edition emphasizes conceptual material—reducing rote memorization, promoting comprehension, and increasing reader friendliness.

Pharmacology can be an unpopular subject because of the vast and rapidly changing area of content. Often, nursing students feel that pharmacology is one of the most difficult classes to master. We hope that this book makes the subject of pharmacology easier and more enjoyable for you to understand by allowing you to focus on the most important umbrella concepts of pharmacology as they relate to nursing care and the safety of patients.

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Finally, we would like to express our gratitude to Richard A. Lehne for his dedication to this book for eight editions. We are honored to be able to continue his work.

Jacqueline Rosenjack Burchum
Laura D. Rosenthal

Contents

UNIT I

INTRODUCTION

CHAPTER 1

Orientation to Pharmacology

By now, you've been hitting the science books for many years and have probably asked yourself, "What's the purpose of all these prerequisite science courses?" In the past, your question may have lacked a satisfying answer. Happily, now you have one: Those courses have provided an excellent background for your studies in pharmacology!

There is a good reason you haven't approached pharmacology before now. Pharmacology is a science that draws on information from multiple disciplines, such as anatomy, physiology, chemistry, microbiology, and psychology. Consequently, before you could study pharmacology, you had to become familiar with these other sciences. Now that you've established the requisite knowledge base, you're finally ready to learn about drugs.

FOUR BASIC TERMS

At this point, I would like to define four basic terms: *drug, pharmacology, clinical pharmacology*, and *therapeutics*. As we consider these definitions, I will indicate the kinds of information that we will and will not discuss in this text.

Drug

A drug is defined as *any chemical that can affect living processes*. By this definition, virtually all chemicals can be considered drugs, because, when exposure is sufficiently high, all chemicals will have some effect on life. Clearly, it is beyond the scope of this text to address all compounds that fit the definition of a drug. Accordingly, rather than discussing all drugs, we will focus primarily on drugs that have therapeutic applications.

Pharmacology

Pharmacology can be defined as *the study of drugs and their interactions with living systems*. Under this definition, pharmacology encompasses the study of the physical and chemical properties of drugs, as well as their biochemical and physiologic effects. In addition, pharmacology includes knowledge of the history, sources, and uses of drugs and knowledge of drug absorption, distribution, metabolism, and excretion. Because pharmacology encompasses such a broad spectrum of information, it would be impossible to address the entire scope of pharmacology in this text. Consequently, we limit consideration to information that is *clinically relevant*.

Clinical Pharmacology

Clinical pharmacology is defined as *the study of drugs in humans*. This discipline includes the study of drugs in *patients* and in *healthy volunteers* (during new drug development). Because clinical pharmacology encompasses all aspects of the interaction between drugs and people, and because our primary interest is the use of drugs to treat patients, clinical pharmacology includes some information that is outside the scope of this text.

Therapeutics

Therapeutics, also known as *pharmacotherapeutics*, is defined as *the use of drugs to diagnose, prevent, or treat disease or to prevent pregnancy*. Alternatively, therapeutics can be defined simply as *the medical use of drugs*.

In this text, therapeutics is our principal concern. Accordingly, much of our discussion focuses on the basic science

that underlies the clinical use of drugs. This information is intended to help you understand how drugs produce their therapeutic and adverse (undesirable) effects; the reasons for giving a particular drug to a particular patient; and the rationale underlying the selection of dosage, route, and schedule of administration. This information will also help you understand the strategies employed to promote beneficial drug effects and to minimize undesired effects. Armed with this knowledge, you will be well prepared to provide drug-related patient care and education. In addition, by making drugs less mysterious, this knowledge should make working with drugs more comfortable and perhaps even more satisfying.

PROPERTIES OF AN IDEAL DRUG

If we were developing a new drug, we would want it to be the best drug possible. To approach perfection, our drug should have certain properties, such as effectiveness and safety. In the discussion that follows, we consider these two characteristics as well as others that an ideal drug might have. Please note, however, that the ideal medication exists in theory only: In reality, *there is no such thing as a perfect drug*. The truth of this statement will become apparent as we consider the properties that an ideal drug should have.

The Big Three: Effectiveness, Safety, and Selectivity

The three most important characteristics that any drug can have are effectiveness, safety, and selectivity.

Effectiveness

An effective drug is one that elicits the responses for which it is given. *Effectiveness is the most important property a drug can have*. Regardless of its other virtues, if a drug is not effective—that is, if it doesn't do what it is intended to do—there is no justification for giving it. Current U.S. law requires that all new drugs be proved effective before being released for marketing.

Safety

A safe drug is defined as one that cannot produce harmful effects—even if administered in very high doses and for a very long time. All drugs have the ability to cause injury, especially with high doses and prolonged use. The chances of producing harmful effects can be reduced by proper drug selection and proper dosing. Nevertheless, the risk of harmful effects can never be eliminated. The following examples illustrate this point:

- Certain anticancer drugs (e.g., cyclophosphamide, methotrexate), at usual therapeutic doses, always increase the risk for serious infection.
- Opioid analgesics (e.g., morphine, meperidine), at high therapeutic doses, can cause potentially fatal respiratory depression.
- Aspirin and related drugs, when taken long term in high therapeutic doses, can cause life-threatening gastric ulceration, perforation, and bleeding.

Clearly, drugs have both benefits and risks. This fact may explain why the Greeks used the word *pharmakon*, which can be translated as both *remedy* and *poison*.

Selectivity

A selective drug is defined as one that elicits *only* the response for which it is given. *There is no such thing as a wholly selective drug because all drugs cause side effects*. Common examples include the drowsiness that can be caused by many antihistamines; the peripheral edema that can be caused by calcium channel blockers; and the sexual dysfunction commonly caused by certain antidepressants.

Additional Properties of an Ideal Drug

Reversible Action

For most drugs, it is important that the effects be reversible. That is, in most cases, we want drug actions to subside within an appropriate time. General anesthetics, for example, would be useless if patients never woke up. Likewise, it is unlikely that oral contraceptives would find wide acceptance if they caused permanent sterility. For a few drugs, however, reversibility is not desirable. With antibiotics, for example, we want the toxicity to microbes to endure.

Predictability

It would be very helpful if, before drug administration, we could know with certainty just how a given patient will respond. Unfortunately, because each patient is unique, the accuracy of predictions cannot be guaranteed. Accordingly, to maximize the chances of eliciting the desired responses, we must tailor therapy to the individual.

Ease of Administration

An ideal drug should be simple to administer: The route should be convenient, and the number of doses per day should be low. Patients with diabetes, who must inject insulin multiple times a day, are not likely to judge insulin ideal. Similarly, nurses who must set up and monitor many intravenous (IV) infusions are unlikely to consider IV drugs ideal.

In addition to convenience, ease of administration has two other benefits: (1) It can enhance patient adherence, and (2) it can decrease risk. Patients are more likely to adhere to a dosing schedule that consists of one daily dose rather than several doses a day. Furthermore, whenever skin integrity is broken, as is the case when drugs are given by injection, there is a risk of infection and injection-site pain and discomfort.

Freedom From Drug Interactions

When a patient is taking two or more drugs, those drugs can interact. These interactions may either augment or reduce drug responses. For example, respiratory depression caused by diazepam [Valium], which is normally minimal, can be greatly *intensified* by alcohol. Conversely, the antibacterial effects of tetracycline can be greatly *reduced* by taking the drug with iron or calcium supplements. Because of the potential for interaction among drugs, when a patient is taking more than one agent, the possible impact of drug interactions must be considered. An ideal drug would not interact with other agents. Unfortunately, few medicines are devoid of significant interactions.

Low Cost

An ideal drug would be easy to afford. The cost of drugs can be a substantial financial burden. As an example, treatment with adalimumab [Humira], a drug for rheumatoid arthritis and Crohn disease, cost more than $112,000 per year in 2021. More commonly, expense becomes a significant factor when a medication must be taken chronically. For example, people with hypertension, arthritis, or diabetes may take medications every day for life. The cumulative expense of such treatment can be exorbitant—even for drugs of moderate price.

Chemical Stability

Some drugs lose effectiveness during storage. Others that may be stable on the shelf can rapidly lose effectiveness when put into solution (e.g., in preparation for infusion). These losses in efficacy result from chemical instability. Because of chemical instability, stocks of certain drugs must be periodically discarded. An ideal drug would retain its activity indefinitely.

Possession of a Simple Generic Name

Generic names of drugs are usually complex, and so they may be difficult to remember and pronounce. As a rule, the brand name for a drug is much simpler than its generic name. Examples of drugs that have complex generic names and simple brand names include acetaminophen [Tylenol], ciprofloxacin [Cipro], and simvastatin [Zocor]. Because generic names are preferable to brand names (for reasons discussed in Chapter 3), an ideal drug should have a generic name that is easy to recall and pronounce.

Because No Drug Is Ideal

From the preceding criteria for ideal drugs, we can see that available medications are not ideal. All drugs have the potential to produce side effects. Drug responses may be difficult to predict and may be altered by drug interactions. Drugs may be expensive, unstable, and hard to administer. Because medications are not ideal, all members of the healthcare team must exercise care to promote therapeutic effects and minimize drug-induced harm.

THE THERAPEUTIC OBJECTIVE

The therapeutic objective of drug therapy is to provide maximum benefit with minimal harm. If drugs were ideal, we could achieve this objective with relative ease; however, because drugs are not ideal, we must exercise skill and care if treatment is to result in more good than harm. As detailed in Chapter 2, you have a critical responsibility in achieving the therapeutic objective. To meet this responsibility, you must understand drugs. The primary purpose of this text is to help you achieve that understanding.

FACTORS THAT DETERMINE THE INTENSITY OF DRUG RESPONSES

Multiple factors determine how an individual will respond to a prescribed dose of a particular drug (Fig. 1.1). By understanding these factors, you will be able to think rationally about how drugs produce their effects. As a result, you will be able to contribute maximally to achieving the therapeutic objective.

Our ultimate concern when administering a drug is the intensity of the response. Working our way up from the bottom of Fig. 1.1, we can see that the intensity of the response is determined by the concentration of a drug at its sites of action. As the figure suggests, the primary determinant of this concentration is the administered dose. When administration is performed correctly, the dose that was given will be the same as the dose that was prescribed. The steps leading from the prescribed dose to the intensity of the response are considered in the sections that follow.

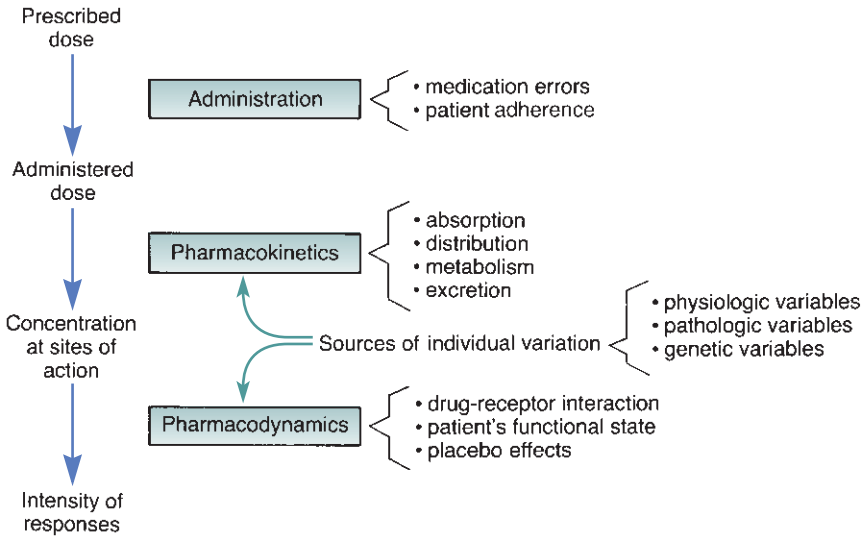

Figure 1.1 ■ **Factors that determine the intensity of drug responses.**

Administration

The drug dosage, route, and timing of administration are important determinants of drug responses. Accordingly, the prescriber will consider these variables with care. Unfortunately, drugs are not always taken or administered as prescribed. The result may be toxicity if the dosage is too high or treatment failure if the dosage is too low.

Sometimes patients do not take medications as prescribed. This is called *poor adherence*. To help minimize errors caused by poor adherence, you should give patients complete instructions about their medication and how to take it.

Medication errors made by hospital staff may result in a drug being administered by the wrong route, in the wrong dose, or at the wrong time; the patient may even be given the wrong drug. These errors can be made by pharmacists, physicians, and nurses. Any of these errors will detract from achieving the therapeutic objective. Medication errors are discussed at length in Chapter 7.

Pharmacokinetics

Pharmacokinetic processes determine how much of an administered dose gets to its sites of action. There are four major pharmacokinetic processes: (1) drug absorption, (2) drug distribution, (3) drug metabolism, and (4) drug excretion. Collectively, these processes can be thought of as the *impact of the body on drugs*. These pharmacokinetic processes are discussed at length in Chapter 4.

Pharmacodynamics

Once a drug has reached its sites of action, pharmacodynamic processes determine the nature and intensity of the response. Pharmacodynamics can be thought of as the *impact of drugs on the body*. In most cases, the initial step leading to a response is the binding of a drug to its receptor. This drug-receptor interaction is followed by a sequence of events that ultimately results in a response. As indicated in Fig. 1.1, the patient's functional state can influence pharmacodynamic processes. For example, a patient who has developed tolerance to morphine will respond less intensely to a particular dose than will a patient who lacks tolerance. Placebo effects also help determine the responses that a drug elicits. Pharmacodynamics is discussed at length in Chapter 5.

Sources of Individual Variation

Characteristics unique to each patient can influence pharmacokinetic and pharmacodynamic processes and, by doing so, can help determine the patient's response to a drug. As indicated in Fig. 1.1, sources of individual variation include physiologic variables (e.g., age, gender, weight); pathologic variables (especially diminished function of the kidneys and liver, the major organs of drug elimination); and genetic variables. Genetic factors can alter the metabolism of drugs and can predispose the patient to unique drug reactions. Because individuals differ from one another, no two patients will respond identically to the same drug regimen. Accordingly, to achieve the therapeutic objective, we must tailor drug therapy to the individual. Individual variation in drug responses is the subject of Chapter 8.

KEY POINTS

- The most important properties of an ideal drug are effectiveness, safety, and selectivity.
- If a drug is not effective, it should not be used.
- Drugs have both benefits and risks.
- There is no such thing as a wholly selective drug; all drugs can cause side effects.
- The objective of drug therapy is to provide maximum benefit with minimum harm.
- Because all patients are unique, drug therapy must be tailored to each individual.

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CHAPTER

2

Application of Pharmacology in Nursing Practice

Our principal goal in this chapter is to answer the question, "Why should a nursing student learn pharmacology?" By addressing this question, I want to give you some extra motivation to study. Why do I think you might need some motivation? Because pharmacology can be challenging, and other topics in nursing are often more alluring. Hopefully, when you complete the chapter, you will be convinced that understanding drugs is essential for nursing practice, and that putting time and effort into learning about drugs will be a good investment.

EVOLUTION OF NURSING RESPONSIBILITIES REGARDING DRUGS

In the past, a nurse's responsibility regarding medications focused on the *Five Rights of Drug Administration* (the Rights)—namely, give the *right drug* to the *right patient* in the *right dose* by the *right route* at the *right time*. More recently, various other rights—*right assessment, right documentation, right evaluation, the patient's rights to education*, and *the patient's right of refusal*—have been recommended for inclusion. Clearly, the original five Rights and their subsequent additions are important. Nevertheless, although these basics are vital, much more is required to achieve the therapeutic objective. The Rights guarantee only that a drug will be administered as prescribed, but correct administration, without additional interventions, cannot ensure that treatment will result in maximum benefit and minimum harm.

The limitations of the Rights can be illustrated with this analogy: The nurse who sees his or her responsibility as being complete after correct drug administration would be like a major league baseball pitcher who felt that his responsibility was over once he had thrown the ball toward the batter. As the pitcher must be ready to respond to the consequences of the interaction between ball and bat, you must be ready to respond to the consequences of the interaction between drug and patient. Put another way, although both the nurse and the pitcher have a clear obligation to deliver their objects in the most appropriate fashion, proper delivery is only the beginning of their responsibilities: *Important events will take place after the object is delivered, and these must be responded to*. Like the pitcher, the nurse can respond rapidly and effectively only by anticipating what the possible reactions to the drug might be.

To anticipate possible reactions, both the nurse and the pitcher require certain kinds of knowledge. Just as the pitcher must understand the abilities of the opposing batter, you must understand the patient and the disorder for which the patient is being treated. As the pitcher must know the most appropriate pitch (e.g., fastball, slider) to deliver in specific circumstances, you must know what medications are appropriate for the patient and must check to ensure that the ordered medication is an appropriate one. Conversely, as the pitcher must know what pitches *not* to throw at a particular batter, you must know what drugs are *contraindicated* for the patient. As the pitcher must know the most likely outcome after the ball and bat interact, you must know the probable consequences of the interaction between drug and patient.

Although this analogy is not perfect (the nurse and patient are on the same team, whereas the pitcher and batter are not), it does help us appreciate that the nurse's responsibility extends well beyond the Rights. Consequently, in addition to the limited information needed to administer drugs in accordance with the Rights, you must acquire a broad base of pharmacologic knowledge to contribute fully to achieving the therapeutic objective.

Nurses, together with healthcare providers and pharmacists, participate in a system of checks and balances designed to promote beneficial effects and minimize harm. Nurses are especially important in this system because it is the nurse who follows the patient's status the most closely. As a result,

you are likely to be the first member of the healthcare team to observe and evaluate drug responses and to intervene if required. To observe and evaluate drug responses, and to intervene rapidly and appropriately, you must know *in advance* the responses that a medication is likely to elicit. The better your knowledge of pharmacology, the better you will be able to *anticipate* drug responses and not simply react to them after the fact.

Within our system of checks and balances, the nurse has an important role as patient advocate. It is your responsibility to detect mistakes made by pharmacists and prescribers. For example, the prescriber may overlook potential drug interactions, be unaware of alterations in the patient's status that would prohibit use of a particular drug, or select the correct drug but order an inappropriate dosage or route of administration. Because the nurse actually administers the drugs, the nurse is the last person to check medications before they are given. Consequently, *you are the patient's last line of defense against medication errors*. It is ethically and legally unacceptable for you to administer a drug that is harmful to the patient—even though the medication has been prescribed by a licensed prescriber and dispensed by a licensed pharmacist. In serving as patient advocate, it is impossible to know too much about drugs.

The two major areas in which you can apply pharmacologic knowledge are patient care and patient education. The application of pharmacology in patient care and patient education is considered in the following two sections.

APPLICATION OF PHARMACOLOGY IN PATIENT CARE

In discussing the applications of pharmacology in patient care, we focus on eight aspects of drug therapy: (1) preadministration assessment, (2) dosage and administration, (3) promoting therapeutic effects, (4) minimizing adverse effects, (5) minimizing adverse interactions, (6) making "as needed" (PRN) decisions, (7) evaluating responses to medication, and (8) managing toxicity.

Preadministration Assessment

All drug therapy begins with assessment of the patient. Assessment has three basic goals: (1) to collect baseline data needed to evaluate therapeutic and adverse (i.e., undesired) responses, (2) to identify high-risk patients, and (3) to assess the patient's capacity for self-care. The first two goals are highly specific for each drug. Accordingly, we cannot achieve these goals without understanding pharmacology. The third goal applies generally to all drugs, and thus it does not usually require specific knowledge of the drug, you are about to give.

Collecting Baseline Data

Baseline data are needed to evaluate both therapeutic and adverse drug responses. Without these data, we would have no way of determining the effectiveness of our drug. For example, if we plan to give a drug to lower blood pressure, we must know the patient's blood pressure before treatment. Similarly, if we are planning to give a drug that can damage the liver, we need to assess baseline liver function to evaluate this potential toxicity. Obviously, to collect appropriate baseline data, we must first know the effects that a drug is likely to produce.

Identifying High-Risk Patients

Multiple factors can predispose an individual to adverse reactions from specific drugs. Important predisposing factors are pathophysiology (especially liver and kidney impairment), genetic factors, drug allergies, and life span considerations, such as pregnancy or very young or advanced age.

Patients with a penicillin allergy provide a dramatic example of those at risk because giving penicillin to such a patient can be fatal. Accordingly, whenever treatment with penicillin is under consideration, we must determine whether the patient has had an allergic reaction to a penicillin in the past and note the type of reaction. If there is a history of true penicillin allergy, an alternative antibiotic should be prescribed.

From the preceding example, we can see that, when planning drug therapy, we must identify patients who are at high risk for reacting adversely. To identify such patients, we use three principal tools: the patient history, physical examination, and laboratory data. Of course, if identification is to be successful, you must know what to look for (i.e., you must know the factors that can increase the risk of severe reactions to the drug in question). Once the high-risk patient has been identified, we can take steps to reduce the risk.

Dosage and Administration

Earlier, we noted the Rights of Drug Administration and agreed on their importance. Although you can implement the Rights without a detailed knowledge of pharmacology, having this knowledge can help reduce your contribution to medication errors. The following examples illustrate this point:

- Certain drugs have more than one indication, and dosage may differ depending on which indication the drug is used for. Aspirin, for example, is given in low doses to relieve pain and in high doses to suppress inflammation. If you do not know about these differences, you might administer too much aspirin to the patient with pain or too little to the patient with inflammation.
- Many drugs can be administered by more than one route, and dosage may differ depending on the route selected. Morphine, for example, may be administered by mouth or by injection. Oral doses are generally much larger than injected doses. Accordingly, if a large dose intended for oral use were to be mistakenly administered by injection, the resulting overdose could prove fatal. The nurse who understands the pharmacology of morphine is unlikely to make this error.
- Certain intravenous (IV) agents can cause severe local injury if the drug extravasates (seeps into the tissues surrounding the IV line). The infusion must be monitored closely, and if extravasation occurs, corrective steps must be taken immediately. The nurse who does not understand the dangers of these drugs will be unprepared to work with them safely.
- The following guidelines can help ensure correct administration:
  - Read the medication order carefully. If the order is unclear, verify it with the prescriber.

- Verify the identity of the patient by comparing the name on the wristband with the name on the drug order or medication administration record.
- Read the medication label carefully. Verify the identity of the drug, the amount of drug (per tablet, volume of liquid, etc.), and its suitability for administration by the intended route.
- Verify dosage calculations.
- Implement any special handling the drug may require.
- Do not administer any drug if you do not understand the reason for its use.

Measures to minimize medication errors are discussed further in Chapter 7.

Promoting Therapeutic Effects

Drug therapy can often be enhanced by nonpharmacologic measures. Examples include (1) enhancing drug therapy of asthma through breathing exercises, biofeedback, and emotional support; (2) enhancing drug therapy of arthritis through exercise, physical therapy, and rest; and (3) enhancing drug therapy of hypertension through weight reduction, smoking cessation, and sodium restriction.

Short-term interventions are also helpful. For instance, mild to moderate pain may be experienced more intensely by the patient who lies slumped down in an uncomfortable bed compared with the patient who is carefully positioned for maximum comfort. Similarly, the pediatric patient with mild to moderate pain who is in a nonstimulating environment may experience the pain more acutely than the patient for whom toys, games, or videos provide distraction.

As a nurse, you will have many opportunities to seek out creative solutions to promote therapeutic effects. You may provide these supportive measures directly or by coordinating the activities of other healthcare providers. Be sure to include these interventions in your patient education to empower patients and their families in optimal self-care.

Minimizing Adverse Effects

All drugs have the potential to produce undesired effects. Common examples include gastric erosion caused by aspirin, sedation caused by older antihistamines, hypoglycemia caused by insulin, and excessive fluid loss caused by diuretics. When drugs are employed properly, the incidence and severity of such events can be reduced. Measures to reduce adverse events include identifying high-risk patients, ensuring proper administration, and teaching patients to avoid activities that might precipitate an adverse event.

When untoward effects cannot be avoided, discomfort and injury can often be minimized by appropriate intervention. For example, timely administration of glucose will prevent brain damage from insulin-induced hypoglycemia. To help reduce adverse effects, you must know the following about the drugs you administer:

- The major adverse effects the drug can produce
- When these reactions are likely to occur
- Early signs that an adverse reaction is developing
- Interventions that can minimize discomfort and harm

Minimizing Adverse Interactions

When a patient is taking two or more drugs, those drugs may interact with one another to diminish therapeutic effects or intensify adverse effects. For example, the ability of oral contraceptives to protect against pregnancy can be reduced by concurrent therapy with carbamazepine (an antiseizure drug), and the risk of thromboembolism from oral contraceptives can be increased by smoking cigarettes.

As a nurse, you can help reduce the incidence and intensity of adverse interactions in several ways. These include taking a thorough drug history, advising the patient to avoid over-the-counter (OTC) drugs that can interact with the prescribed medication, monitoring for adverse interactions *known* to occur between the drugs the patient is taking, and being alert to the possibility of *as-yet-unknown* interactions.

Making PRN Decisions

PRN stands for *pro re nata*, a Latin phrase meaning *as needed*. A PRN medication order is one in which the nurse has discretion regarding when to give a drug and, in some situations, how much of the drug to give. PRN orders are common for drugs that promote sleep, relieve pain, and reduce anxiety. To implement a PRN order rationally, you must know the reason the drug is prescribed and be able to assess the patient's medication needs. Clearly, the better your knowledge of pharmacology, the better your PRN decisions are likely to be.

Evaluating Responses to Medication

Evaluation is one of the most important aspects of drug therapy. After all, this is the process that tells us whether a drug is producing a benefit or is causing harm. Because the nurse follows the patient's status most closely, the nurse is in the best position to evaluate therapeutic responses.

To make an evaluation, you must know the rationale for treatment and the nature and time course of the intended response. When desired responses do *not* occur, it may be essential to identify the reason quickly so that timely implementation of alternative therapy may be ordered.

When evaluating responses to a drug that has more than one application, you can do so only if you know the specific indication for which the drug is being used. Nifedipine, for example, is given for both hypertension and angina pectoris. When the drug is used for hypertension, you should monitor for a reduction in blood pressure. In contrast, when this drug is used for angina, you should monitor for a reduction in chest pain. Clearly, if you are to make the proper evaluation, you must understand the reason for drug use.

Managing Toxicity

Some adverse drug reactions are extremely dangerous. If toxicity is not diagnosed early and responded to quickly, irreversible injury or death can result. To minimize harm, you must know the early signs of toxicity and the procedure for toxicity management.

APPLICATION OF PHARMACOLOGY IN PATIENT EDUCATION

Very often, the nurse is responsible for educating patients about medications. In your role as educator, you must give the patient the following information:

- Drug name and therapeutic category (e.g., penicillin is an antibiotic)
- Dosage
- Dosing schedule
- Route and technique of administration
- Expected therapeutic response, and when it should develop
- Nondrug measures to enhance therapeutic responses
- Duration of treatment
- Method of drug storage
- Symptoms of major adverse effects, and measures to minimize discomfort and harm
- Major adverse drug-drug and drug-food interactions
- Whom to contact in the event of therapeutic failure, severe adverse reactions, or severe adverse interactions

To communicate this information effectively and accurately, you must first understand it. That is, to be a good drug educator, you must know pharmacology.

In the following discussion, we consider the relationship between patient education and the following aspects of drug therapy: dosage and administration, promoting therapeutic effects, minimizing adverse effects, and minimizing adverse interactions.

Dosage and Administration

Drug Name

The patient should know the name of the medication he or she is taking. If the drug has been prescribed by brand name, the patient should be given its generic name, too. This information will reduce the risk for overdose that can result when a patient fails to realize that two prescriptions that bear different names actually contain the same medicine.

Dosage and Schedule of Administration

Patients must be told how much of a drug to take and when to take it. For some medications, dosage must be adjusted by the patient. Insulin is a good example. For insulin therapy to be most beneficial, the patient may need to adjust doses to accommodate changes in diet and subsequent glucose levels.

With PRN medications, the schedule of administration is not fixed. Rather, these drugs are taken as conditions require. For example, some people with asthma experience exercise-induced bronchospasm. To minimize such attacks, they can take supplementary medication before anticipated exertion. It is your responsibility to teach patients when PRN drugs should be taken.

The patient should also know what to do if a dose is missed. With certain oral contraceptives, for example, if one dose is missed, the omitted dose should be taken together with the next scheduled dose. If three or more doses are missed, however, a new cycle of administration must be initiated.

Patient Adherence

Adherence—also known as compliance or concordance—may be defined as the extent to which a patient's behavior coincides with medical advice. If we are to achieve the therapeutic objective, adherence to the prescribed drug regimen is essential. Drugs that are self-administered in the wrong dose, by the wrong route, or at the wrong time cannot produce maximum benefit and may even prove harmful. Obviously, successful therapy requires active and informed participation by the patient. By educating patients about the drugs they are taking, you can help elicit the required participation.

Some patients have difficulty remembering whether they have taken their medication. Possible causes include mental illness, advanced age, and complex regimens. To facilitate adherence for these patients, one solution is to provide the patient with a pill organizer that has separate compartments for each day of the week, and then to teach the patient or family member to load the compartments weekly. To determine whether a dose of medication has been taken, patients and their families can simply check the day of the week in the pill organizer to see whether the drugs have been removed.

Technique of Administration

Patients must be taught how to administer their drugs. This is especially important for routes that may be unfamiliar (e.g., sublingual for nitroglycerin) and for techniques that can be difficult (e.g., subcutaneous injection of insulin). Patients taking oral medications may require special instructions. For example, some oral preparations must not be chewed or crushed; some should be taken with fluids; and some should be taken with meals, whereas others should be taken on an empty stomach. Careful attention must be paid to the patient who, because of disability (e.g., visual or intellectual impairment, limited manual dexterity), may find self-medication difficult.

Duration of Drug Use

Just as patients must know when to take their medicine, they must know when to stop. In some cases (e.g., treatment of acute pain), patients should discontinue drug use as soon as symptoms subside. In other cases (e.g., treatment of hypertension), patients should know that therapy will probably continue lifelong. For some conditions (e.g., gastric ulcers), medication may be prescribed for a specific time interval, after which the patient should return for reevaluation.

Drug Storage

Certain medications are chemically unstable and deteriorate rapidly if stored improperly. Patients who are using unstable drugs must be taught how to store them correctly (e.g., under refrigeration, in a lightproof container). All drugs should be stored where children cannot reach them.

Promoting Therapeutic Effects

To participate fully in achieving the therapeutic objective, patients must know the nature and time course of expected beneficial effects. With this knowledge, patients can help evaluate the success or failure of treatment. By recognizing treatment failure, the informed patient will know to return to the healthcare provider for changes in therapy.

With some drugs, such as those used to treat depression and schizophrenia, beneficial effects may take several weeks to become maximal. Awareness that treatment may not produce immediate results allows the patient to have realistic expectations and helps reduce anxiety about therapeutic failure.

As noted, nondrug measures can complement drug therapy. For example, although drugs are useful in managing high cholesterol, exercise and diet are also important. Teaching the patient about nondrug measures can greatly increase the chances of success.

Minimizing Adverse Effects

Knowledge of adverse drug effects will enable the patient to avoid some adverse effects and minimize others through early detection. The following examples underscore the value of educating patients about the undesired effects of drugs:

- Insulin overdose can cause blood glucose levels to drop precipitously. Early signs of hypoglycemia include shakiness, perspiration, and anxiety. The patient who has been taught to recognize these early signs can respond by ingesting glucose or other fast-acting carbohydrate-rich foods, thereby restoring blood sugar to a safe level. In contrast, the patient who fails to recognize evolving hypoglycemia and does not ingest glucose or similar substances may become comatose and may even die.
- Many anticancer drugs predispose patients to acquiring serious infections. The patient who is aware of this possibility can take steps to avoid contagion by avoiding contact with people who have an infection and by avoiding foods likely to contain pathogens. In addition, the informed patient is in a position to notify the healthcare prescriber at the first sign that an infection is developing, thereby allowing early treatment. In contrast, the patient who has not received adequate education is at increased risk for illness or death from an untreated infectious disease.
- Some side effects, although benign, can be disturbing if they occur without warning. For example, rifampin (a drug for tuberculosis) imparts a harmless red-orange color to urine, sweat, saliva, and tears. Your patient will appreciate knowing about this in advance.

Minimizing Adverse Interactions

Patient education can help avoid hazardous drug-drug and drug-food interactions. For example, phenelzine (an antidepressant) can cause dangerous elevations in blood pressure if taken in combination with certain drugs (e.g., amphetamines) or certain foods (e.g., sauerkraut, aged or smoked meats, most cheeses). Accordingly, it is essential that patients taking phenelzine are given specific and emphatic instructions regarding the drugs and foods they must avoid.

APPLICATION OF THE NURSING PROCESS IN DRUG THERAPY

The nursing process is a conceptual framework that nurses employ to guide healthcare delivery. In this section, we consider how the nursing process can be applied in drug therapy.

Review of the Nursing Process

Before discussing the nursing process as it applies to drug therapy, we need to review the process itself. Because you are probably familiar with the process already, this review is brief.

In its simplest form, the nursing process can be viewed as a cyclic procedure that has five basic steps: (1) assessment, (2) analysis (including nursing diagnoses), (3) planning, (4) implementation, and (5) evaluation.

Assessment

Assessment consists of collecting data about the patient. These data are used to identify actual and potential health problems. The database established during assessment provides a foundation for subsequent steps in the process. Important methods of data collection are the patient interview, medical and drug-use histories, the physical examination, observation of the patient, and findings of screening or diagnostic studies (e.g., laboratory and radiologic test results).

Analysis or Nursing Diagnoses

In this step, the nurse analyzes information in the database to determine actual and potential health problems. These problems may be physiologic, psychologic, or sociologic. Problems may be stated in the form of a *nursing diagnosis*,[a] which can be defined as an actual or potential health problem that nurses are qualified and licensed to treat.

A complete nursing diagnosis consists of three statements: (1) a statement of the patient's actual or potential health problem, followed by (2) a statement of the problem's probable cause or risk factors, and (3) the signs, symptoms, or other evidence of the problem. (This third component is omitted for potential problems.) Typically, the statements are separated by the phrases "related to" and "as evidenced by," as in this example of a drug-associated nursing diagnosis: "noncompliance with the prescribed regimen [the problem] related to complex medication administration schedule [the cause] as evidenced by missed drug doses and patient's statement that the schedule is confusing [the evidence]."

Planning

In the planning step, the nurse delineates specific interventions directed at solving or preventing the problems identified in the analysis phase. The plan must be individualized for each patient. When creating a care plan, the nurse must define goals, set priorities, identify nursing interventions, and establish criteria for evaluating success. In addition to nursing interventions, the plan should include interventions performed by other healthcare providers. Planning is an ongoing process that must be modified as new data are gathered and the patient's situation changes.

Implementation

Implementation begins with carrying out the interventions identified during planning. Some interventions are collaborative, whereas others are independent. Collaborative interventions require a healthcare provider's order, whereas independent interventions do not. In addition to carrying out interventions, implementation involves coordinating the actions of other members of the healthcare team. Implementation is completed by observing and documenting the outcomes of treatment.

Evaluation

Evaluation is performed to determine the degree to which treatment has succeeded. By evaluating the outcomes of

[a]Nursing diagnosis is not taught in some schools and colleges of nursing. Information is provided here for those programs that include this information.

treatment, nurses identify those interventions that should be continued, those that should be discontinued, and potential new interventions that may be implemented. Evaluation is accomplished by analyzing the data collected after implementation. This step completes the initial cycle of the nursing process and provides the basis for beginning the cycle anew.

Applying the Nursing Process in Drug Therapy

Having reviewed the nursing process itself, we can now discuss the process as it pertains to drug therapy. Recall that the overall objective in drug therapy is to produce maximum benefit with minimum harm.

Preadministration Assessment

A preadministration assessment establishes the baseline data needed to tailor drug therapy to the individual. By identifying the variables that can affect an individual's response to a drug, we can adapt treatment so as to maximize benefits and minimize harm. Preadministration assessment has four basic goals:

- Collection of baseline data needed to evaluate therapeutic effects
- Collection of baseline data needed to evaluate adverse effects
- Identification of high-risk patients
- Assessment of the patient's capacity for self-care

The first three goals are specific to the particular drug being used. Accordingly, to achieve these goals, you must know the pharmacology of the drug under consideration. The fourth goal applies more or less equally to all drugs—although this goal may be more critical for some drugs than others.

Important methods of data collection include interviewing the patient and family, observing the patient, performing a physical examination, checking the results of laboratory and radiologic tests, and taking the patient's medical and drug histories. The drug history should include prescription drugs, OTC drugs, herbal remedies, and drugs taken for nonmedical or recreational purposes (e.g., alcohol, nicotine, caffeine, and illegal drugs). Prior adverse drug reactions should be noted, including drug allergies and idiosyncratic reactions (i.e., reactions unique to the individual).

Baseline Data Needed to Evaluate Therapeutic Effects. Drugs are administered to achieve a desired response. To know whether we have produced that response, we need to establish baseline measurements of the parameter that therapy is directed at changing. For example, if we are giving a drug to lower blood pressure, we need to know what the patient's blood pressure was before treatment. Without this information, we have no basis for determining the effectiveness of our drug.

Baseline Data Needed to Evaluate Adverse Effects. All drugs have the ability to produce undesired effects. In most cases, the adverse effects that a particular drug can produce are known. In many cases, the development of an adverse effect will be completely obvious in the absence of any baseline data. For example, we do not need special baseline data to know that hair loss after cancer chemotherapy was caused by the drug. In other cases, however, baseline data are needed to determine whether an adverse effect has occurred. For example, some drugs can impair liver function. To know whether a drug has compromised liver function, we need to know the state of liver function before drug use. Without this information, we cannot tell from later measurements whether liver dysfunction was preexisting or caused by the drug.

Identification of High-Risk Patients. Because of individual characteristics, a particular patient may be at high risk for experiencing an adverse response to a particular drug. Just which individual characteristics will predispose a patient to an adverse reaction depends on the drug under consideration. For example, if a drug is eliminated from the body primarily by renal excretion, an individual with impaired kidney function will be at risk for having this drug accumulate to a toxic level. Similarly, if a drug is eliminated by the liver, an individual with impaired liver function will be at risk for having that drug accumulate to a toxic level.

Multiple factors can increase the patient's risk for adverse reactions to a particular drug. Impaired liver and kidney function were just mentioned. Other factors include age, body composition, pregnancy, diet, genetic heritage, other drugs being used, and practically any pathophysiologic condition. These factors are discussed at length in Chapters 6 through 11.

When identifying factors that put the patient at risk, you should distinguish between factors that put the patient at extremely high risk versus factors that put the patient at moderate or low risk. The terms *contraindication* and *precaution* are used for this distinction. A *contraindication* is defined as a condition that prohibits the use of a particular drug under all but the most critical of circumstances. For example, a previous severe allergic reaction to penicillin would be a contraindication to using penicillin again—unless the patient has a life-threatening infection that cannot be effectively treated with another antibiotic. In this situation, in which the patient *will* die if the drug *is not* administered yet the patient *may* die if the drug *is* administered, the healthcare provider may decide to give the penicillin along with other drugs and measures to decrease the severity of the allergic reaction. A *precaution*, by contrast, can be defined as a condition that significantly increases the risk for an adverse reaction to a particular drug but not to a degree that is life-threatening. For example, sedating antihistamines pose a risk to elderly patients who are at risk of falling, which would constitute a precaution against using this drug in older adults. That is, the drug may be used, but greater than normal caution must be exercised. Preferably, an alternative nonsedating antihistamine would be selected.

Assessment of the Patient's Capacity for Self-Care. If drug therapy is to succeed, the outpatient must be willing and able to self-administer medication as prescribed. Accordingly, his or her capacity for self-care must be determined. If the assessment reveals that the patient is incapable of self-medication, alternative care must be arranged.

Multiple factors can affect the capacity for self-care and the probability of adhering to the prescribed regimen. Patients with reduced visual acuity or limited manual dexterity may be unable to self-medicate, especially if the technique for administration is complex. Patients with limited intellectual ability may be incapable of understanding or remembering what they are supposed to do. Patients with severe mental illness (e.g., depression, schizophrenia) may lack the understanding or motivation needed to self-medicate. Some patients may lack the money to pay for drugs. Others may fail to take

medications as prescribed because of individual or cultural attitudes toward drugs. For example, a common cause for failed self-medication is a belief that the drug was simply not needed in the dosage prescribed. A thorough assessment will identify all of these factors, thereby enabling you to account for them when formulating nursing diagnoses and the patient care plan.

Analysis and Nursing Diagnoses

With respect to drug therapy, the analysis phase of the nursing process has three objectives. First, you must judge the appropriateness of the prescribed regimen. Second, you must identify potential health problems that the drug might cause. Third, you must determine whether your assessment of the patient's capacity for self-care identified an impaired ability for self-care.

As the last link in the patient's chain of defense against inappropriate drug therapy, you must analyze the data collected during the assessment to determine whether the proposed treatment has a reasonable likelihood of being effective and safe. This judgment is made by considering the medical diagnosis, the known actions of the prescribed drug, the patient's prior responses to the drug, and the presence of contraindications to the drug. You should question the drug's appropriateness if (1) the drug has no actions that are known to benefit individuals with the patient's medical diagnosis, (2) the patient failed to respond to the drug in the past, (3) the patient had a serious adverse reaction to the drug in the past, or (4) the patient has a condition or is using a drug that contraindicates the prescribed drug. If any of these conditions apply, you should consult with the prescriber to determine whether the drug should be given.

The analysis must identify potential adverse effects and drug interactions. This is accomplished by integrating knowledge of the drug under consideration and the data collected during the assessment. Knowledge of the drug will indicate adverse effects that practically all patients are likely to experience. Data on the individual patient will indicate additional adverse effects and interactions to which the particular patient is predisposed. Once potential adverse effects and interactions have been identified, pertinent nursing diagnoses can be formulated. For example, if treatment is likely to cause respiratory depression, an appropriate nursing diagnosis would be "risk for impaired gas exchange related to drug therapy." Table 2.1 presents additional examples of nursing diagnoses that can be readily derived from your knowledge of adverse effects and interactions that treatment may cause.

The analysis must characterize the patient's capacity for self-care. The analysis should indicate potential impediments to self-care (e.g., visual impairment, reduced manual dexterity, impaired cognitive function, insufficient understanding of the prescribed regimen) so that these factors can be addressed in the care plan. To varying degrees, nearly all patients will be unfamiliar with self-medication and the drug regimen. Accordingly, a nursing diagnosis applicable to almost every patient is "knowledge deficit related to the drug regimen."

Planning

Planning consists of defining goals, establishing priorities, identifying specific interventions, and establishing criteria for evaluating success. Good planning will allow you to promote beneficial drug effects. Of equal or greater importance, good planning will allow you to anticipate adverse effects, rather than react to them after the fact.

Defining Goals. In all cases, the goal of drug therapy is to produce maximum benefit with minimum harm. That is, we want to employ drugs in such a way as to maximize therapeutic responses, while preventing or minimizing adverse reactions and interactions. The objective of planning is to formulate ways to achieve this goal.

Setting Priorities. Priority setting requires knowledge of the drug under consideration and the patient's unique characteristics—and even then, setting priorities can be difficult. The highest priority is given to life-threatening conditions (e.g., anaphylactic shock, ventricular fibrillation). These may be drug-induced or the result of disease. High priority is also given to reactions that cause severe, acute discomfort and to reactions that can result in long-term harm. Because we cannot manage all problems simultaneously, less severe problems are relegated to lower positions when prioritizing care.

Identifying Interventions. The heart of planning is the identification of nursing interventions. For medication purposes, these interventions can be divided into four major groups:

TABLE 2.1 ▪ Examples of Nursing Diagnoses That Can Be Derived From Knowledge of Adverse Drug Effects

Drug	Adverse Effect	Related Nursing Diagnosis
Amphetamine	CNS stimulation	Disturbed sleep pattern related to drug-induced CNS excitation.
Aspirin	Gastric erosion	Pain related to aspirin-induced gastric erosion.
Atropine	Urinary retention	Urinary retention related to drug therapy.
Bethanechol	Stimulation of GI smooth muscle	Bowel incontinence related to a drug-induced increase in bowel motility.
Cyclophosphamide	Reduction in white blood cell counts	Risk for infection related to drug-induced neutropenia.
Digoxin	Dysrhythmias	Ineffective tissue perfusion related to drug-induced cardiac dysrhythmias.
Furosemide	Excessive urine production	Deficient fluid volume related to drug-induced diuresis.
Gentamicin	Damage to the eighth cranial nerve	Disturbed sensory perception: hearing impairment related to drug therapy.
Glucocorticoids	Thinning of the skin	Impaired skin integrity related to drug therapy.
Haloperidol	Involuntary movements	Low self-esteem related to drug-induced involuntary movements.
Propranolol	Bradycardia	Decreased cardiac output related to drug-induced bradycardia.
Warfarin	Bleeding	Risk for injury related to drug-induced bleeding.

CNS, Central nervous system; *GI,* gastrointestinal.

(1) drug administration, (2) interventions to enhance therapeutic effects, (3) interventions to minimize adverse effects and interactions, and (4) patient education (which encompasses information in the first three groups).

When planning drug administration, you must consider the dosage and route of administration, as well as less obvious factors, including the timing of administration with respect to meals and with respect to the administration of other drugs. Timing with respect to side effects is also important. For example, if a drug causes sedation, it may be desirable to give the drug at bedtime, rather than in the morning; conversely, a diuretic, which increases urination, is better given earlier in the morning rather than at bedtime.

Nondrug measures can help promote therapeutic effects and should be included in the plan. For example, drug therapy for hypertension can be combined with weight loss (in overweight patients), salt restriction, and smoking cessation.

Interventions to prevent or minimize adverse effects are of obvious importance. When planning these interventions, you should distinguish between reactions that develop quickly and reactions that are delayed. A few drugs can cause severe adverse reactions (e.g., anaphylactic shock) shortly after administration. When planning to administer such a drug, you should ensure that facilities for managing possible reactions are immediately available. Delayed reactions can often be minimized, if not avoided entirely. The plan should include interventions to do so.

Well-planned patient education is central to success. Patient education is discussed at length earlier in this chapter.

Establishing Criteria for Evaluation. The need for objective criteria by which to measure desired drug responses is obvious: Without such criteria, we could not determine how well our drug achieved the therapeutic objective. As a result, we would have no rational basis for making dosage adjustments or for deciding whether a drug should be continued.

Criteria for evaluation vary depending on the drug and its purpose. For an analgesic, the criterion for evaluation is a decrease or resolution of pain. For the patient prescribed thyroid hormones for hypothyroidism, a criterion for evaluation is typically a laboratory test (e.g., thyroid stimulating hormone level and free thyroxine level within normal range). Conversely, for the patient prescribed an antihypertensive, a criterion for evaluation may be a target blood pressure goal. Often, there are several criteria for evaluating a given drug.

If the drug is to be used on an outpatient basis, follow-up visits for evaluation should be planned. It is important to educate the patient on the importance of these visits even if the patient is feeling well.

Implementation

Implementation of the care plan in drug therapy has four major components: (1) drug administration, (2) patient education, (3) interventions to promote therapeutic effects, and (4) interventions to minimize adverse effects. These critical nursing activities are discussed at length in the previous section.

Evaluation

Over the course of drug therapy, the patient must be evaluated for (1) therapeutic responses, (2) adverse drug reactions and interactions, (3) adherence to the prescribed regimen, and (4) satisfaction with treatment. How frequently evaluations are performed depends on the expected time course of therapeutic and adverse effects. Like assessment, evaluation is based on laboratory tests, observation of the patient, physical examination, and patient interviews. The conclusions drawn during the evaluation provide the basis for modifying nursing interventions and the drug regimen.

Therapeutic responses are evaluated by comparing the patient's current status with the baseline data. To evaluate treatment, you must know the reason for drug use, the criteria for evaluation, and the expected time course of responses (some drugs act within minutes, whereas others may take weeks to produce beneficial effects).

The need to anticipate and evaluate adverse effects is self-evident. To make these evaluations, you must know which adverse effects are likely to occur, how they manifest, and their probable time course. The method of monitoring is determined by the expected effect. For example, if hypotension is expected, blood pressure is monitored; if constipation is expected, bowel function is monitored. Because some adverse effects can be fatal in the absence of timely detection, it is impossible to overemphasize the importance of monitoring and being prepared for rapid intervention.

Evaluation of adherence is desirable in all patients—and is especially valuable when therapeutic failure occurs or when adverse effects are unexpectedly severe. Methods of evaluating adherence include measuring plasma drug levels, interviewing the patient, and counting pills. The evaluation should determine whether the patient understands when to take the medication, what dose to take, and the technique of administration, as well as whether the patient is taking the drug(s) exactly as prescribed.

Patient satisfaction with drug therapy increases quality of life and promotes adherence. If the patient is dissatisfied, an otherwise effective regimen may not be taken as prescribed. Factors that can cause dissatisfaction include unacceptable side effects, inconvenient dosing schedule, difficulty of administration, and high cost. When evaluation reveals dissatisfaction, an attempt should be made to alter the regimen to make it more acceptable.

Use of a Modified Nursing Process Format to Summarize Nursing Implications

Throughout this text, nursing implications are *integrated into the body of each chapter*. The reason for integrating nursing information with basic science information is to reinforce the relationship between pharmacologic knowledge and nursing practice. In addition to being integrated, nursing implications are *summarized at the end of most chapters* under the heading "Summary of Major Nursing Implications." The purpose of these summaries is to provide a concise and readily accessible reference on patient care and patient education related to specific drugs and drug families.

The format employed for summarizing nursing implications reflects the nursing process. Some headings have been modified to accommodate the needs of pharmacology instruction and to keep the summaries concise.

KEY POINTS

- Nursing responsibilities with regard to drugs extend far beyond the Rights of Drug Administration.
- You are the patient's last line of defense against medication errors.
- Your knowledge of pharmacology has a wide variety of practical applications in patient care and patient education.
- By applying your knowledge of pharmacology, you will make a large contribution to achieving the therapeutic objective of maximum benefit with minimum harm.
- Application of the nursing process in drug therapy is directed at individualizing treatment, which is critical to achieving the therapeutic objective.
- The goal of preadministration assessment is to gather data needed for (1) the evaluation of therapeutic and adverse effects, (2) the identification of high-risk patients, and (3) an assessment of the patient's capacity for self-care.
- The analysis and diagnosis phase of treatment is directed at (1) judging the appropriateness of the prescribed therapy, (2) identifying potential health problems treatment might cause, and (3) characterizing the patient's capacity for self-care.
- Planning is directed at (1) defining goals, (2) establishing priorities, and (3) establishing criteria for evaluating success.
- In the evaluation stage, the objective is to evaluate: (1) therapeutic responses, (2) adverse reactions and interactions, (3) patient adherence, and (4) patient satisfaction with treatment.

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CHAPTER

3

Drug Regulation, Development, Names, and Information

In this chapter, we complete our introduction to pharmacology by considering five diverse but important topics. These are (1) drug regulation, (2) new drug development, (3) the annoying problem of drug names, (4) over-the-counter (OTC) drugs, and (5) sources of drug information.

LANDMARK DRUG LEGISLATION

The history of drug legislation in the United States reflects an evolution in our national posture toward regulating the pharmaceutical industry. That posture has changed from one of minimal control to one of extensive control. For the most part, increased regulation has been beneficial, resulting in safer and more effective drugs.

The first American law to regulate drugs was the *Federal Pure Food and Drug Act* of 1906. This law set standards for drug quality and purity in addition to strength. It specifically focused on product labeling and required that any variations from the standards be placed on the label.

The *Food, Drug, and Cosmetic Act*, passed in 1938, was the first legislation to address drug safety. The motivation behind the law was a tragedy in which more than 100 people died after using a new medication. The lethal preparation contained sulfanilamide, an antibiotic, plus diethylene glycol as a solubilizing agent. Tests showed that the solvent was the cause of death. (Diethylene glycol is commonly used as automotive antifreeze.) To reduce the chances of another such tragedy, Congress required that all new drugs undergo testing for safety. The results of these tests were to be reviewed by the *U.S. Food and Drug Administration* (FDA), and only those drugs judged safe would receive FDA approval for marketing.

In 1962, Congress passed the *Harris-Kefauver Amendments* to the Food, Drug, and Cosmetic Act. This bill was created in response to the thalidomide tragedy that occurred in Europe in the early 1960s. Thalidomide is a sedative now known to cause birth defects and fetal death. Because the drug was used widely by pregnant patients, thousands of infants were born with phocomelia, a rare birth defect characterized by the gross malformation or complete absence of arms or legs. This tragedy was especially poignant in that it resulted from nonessential drug use: The women who took thalidomide could have managed their conditions without it. Thalidomide was not a problem in the United States because the drug never received approval by the FDA.

Because of the European experience with thalidomide, the Harris-Kefauver Amendments sought to strengthen all aspects of drug regulation. A major provision of the bill required that drugs be proved *effective* before marketing. Remarkably, this was the first law to demand that drugs actually offer some benefit. The new Act also required that all drugs that had been introduced between 1932 and 1962 undergo testing for effectiveness; any drug that failed to prove useful would be withdrawn. Lastly, the Harris-Kefauver Amendments established rigorous procedures for testing new drugs. These procedures are discussed later in this chapter under *New Drug Development*.

In 1970, Congress passed the *Controlled Substances Act* (Title II of the Comprehensive Drug Abuse Prevention and Control Act). This legislation set rules for the manufacture and distribution of drugs considered to have the potential for abuse. One provision of the law defines five categories of controlled substances, referred to as Schedules I, II, III, IV, and V. Drugs in Schedule I have no accepted medical use in the United States and are deemed to have a high potential for abuse. Examples include heroin, mescaline, and lysergic acid diethylamide (LSD). Drugs in Schedules II through V have accepted medical applications but also have a high potential for abuse. The abuse potential of these agents becomes progressively less as we proceed from Schedule II to Schedule V. The Controlled Substances Act is discussed further in Chapter 40.

In 1992, FDA regulations were changed to permit *accelerated approval* of drugs for acquired immunodeficiency syndrome (AIDS) and cancer. Under these guidelines, a drug could be approved for marketing before the completion of Phase III trials (discussed later in the chapter), provided that rigorous follow-up studies (Phase IV trials) were performed. The rationale for this change was that (1) medications are needed, even if their benefits may be marginal, and (2) the unknown risks associated with early approval are balanced

by the need for more effective drugs. Although accelerated approval seems like a good idea, in actual practice, it has two significant drawbacks. First, manufacturers often fail to conduct or complete the required follow-up studies. Second, if the follow-up studies—which are more rigorous than the original—fail to confirm a clinical benefit, the guidelines have no clear mechanism for removing the drug from the market.

The *Prescription Drug User Fee Act* (PDUFA), passed in 1992, was a response to complaints that the FDA was taking too long to review applications for new drugs. Under the Act, drug sponsors pay the FDA fees that are used to fund additional reviewers. In return, the FDA must adhere to strict review timetables. Because of the PDUFA, new drugs now reach the market much sooner than in the past.

The *Food and Drug Administration Modernization Act* (FDAMA) of 1997—an extension of the PDUFA—called for widespread changes in FDA regulations. Implementation is in progress. For health professionals, four provisions of the Act are of particular interest:

- The fast-track system created for AIDS drugs and cancer drugs now includes drugs for other serious and life-threatening illnesses.
- Manufacturers who plan to stop making a drug must inform patients at least 6 months in advance, thereby giving them time to find another source.
- A clinical trial database is required for drugs directed at serious or life-threatening illnesses. These data allow clinicians and patients to make informed decisions about using experimental drugs.
- Drug companies can now give prescribers journal articles and certain other information regarding off-label uses of drugs. (An *off-label use* is a use that has not been evaluated by the FDA.) Before the new Act, clinicians were allowed to prescribe a drug for an off-label use, but the manufacturer was not allowed to promote the drug for that use—even if promotion was limited to providing potentially helpful information, including reprints of journal articles. In return for being allowed to give prescribers information regarding off-label uses, manufacturers must promise to do research to support the claims made in the articles.

Two laws—the *Best Pharmaceuticals for Children Act* (BPCA), passed in 2002, and the *Pediatric Research Equity Act* (PREA) of 2003—were designed to promote much-needed research on drug efficacy and safety in children. The BPCA offers a 6-month patent extension to manufacturers who evaluate a drug already on the market for its safety, efficacy, and dosage in children. The PREA gives the FDA the power, for the first time, to require drug companies to conduct pediatric clinical trials on new medications that might be used by children. (In the past, drugs were not tested in children, so there was a general lack of reliable information upon which to base therapeutic decisions.)

In 2007, Congress passed the *FDA Amendments Act* (FDAAA), the most important legislation on drug safety since the Harris-Kefauver Amendments of 1962. The FDAAA expands the mission of the FDA to include rigorous oversight of drug safety *after* a drug has been approved. (Before this Act, the FDA focused on drug efficacy and safety *before* approval but had limited resources and authority to address drug safety after a drug was released for marketing.) Under the new law, the FDA has the legal authority to require postmarketing safety studies, to order changes in a drug's label to include new safety information, and to restrict distribution of a drug based on safety concerns. In addition, the FDA was required to establish an active postmarketing risk surveillance system, mandated to include 25 million patients by July 2010 and 100 million by July 2012. Because of the FDAAA, adverse effects that were not discovered before drug approval came to light much sooner than in the past, and the FDA now has the authority to take action (e.g., limit distribution of a drug) if postmarketing information shows a drug to be less safe than previously understood.

In 2009, Congress passed the *Family Smoking Prevention and Tobacco Control Act*, which, at long last, allows the FDA to regulate cigarettes, which are responsible for about one in five deaths in the United States each year. Under the Act, the FDA was given the authority to strengthen advertising restrictions, including a prohibition on marketing to youth; require revised and more prominent warning labels; require disclosure of all ingredients in tobacco products and restrict harmful additives; and monitor nicotine yields and mandate gradual reduction of nicotine to nonaddictive levels. The *Comprehensive Addiction and Recovery Act (CARA) of 2016* and the *Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act of 2018* were developed to combat a nationwide opioid epidemic by addressing the crisis from multiple approaches. To that end, they provide grants to support efforts directed toward prevention, treatment, and rehabilitation/recovery; opioid overdose reversal by first responders, law enforcement officers, and families; and the establishment of opioid recovery centers. Implications for nursing are significant because nurses have important roles in the expanded drug education and other prevention programs and in drug addiction treatment and recovery programs. Additionally, nurses are often in roles in which they serve as first responders.

HAZARDOUS DRUG EXPOSURE

Exposure to certain drugs can be dangerous for nurses and other healthcare workers who handle them. It is imperative to ensure your own safety as well as the safety of your patients.

The National Institute for Occupational Safety and Health (NIOSH), established in 1970, has the responsibility to promote and enhance worker safety. Thus NIOSH identifies which of the thousands of drugs are hazardous for handling and publishes guidance on the safe handling of these drugs.

In their publication *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016* (available online at www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf), NIOSH identifies a drug as hazardous for handling if it meets one or more of the following criteria:

- Carcinogenicity
- Teratogenicity or developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses
- Genotoxicity
- New drugs with structure and toxicity profiles similar to drugs previously determined to be hazardous

It is probably not surprising to find that antineoplastic drugs (drugs that kill cancer cells) are included in the list, but

common drugs such as oral contraceptives (birth control pills) are also included. You will learn about these throughout the textbook, and the full listing is also available in the NIOSH publication.

NIOSH provides instructions on how nurses and other healthcare workers can use protective equipment and environmental controls to prevent the potentially harmful effects associated with these drugs. These guidelines are provided in Table 3.1.

NEW DRUG DEVELOPMENT

The development and testing of new drugs is an expensive and lengthy process, requiring 10 to 15 years for completion. Of the thousands of compounds that undergo testing, only a few enter clinical trials, and of these, only one in five gains approval. According to an article in the May 2016 issue of the *Journal of Health Economics*, the cost of developing a new drug and gaining approval for marketing averages $2.558 billion for each approved drug.

Rigorous procedures for testing have been established so that newly released drugs can be both safe and effective. Unfortunately, although testing can determine effectiveness, it cannot guarantee that a new drug will be safe. For example, significant adverse effects may evade detection during testing, only to become apparent after a new drug has been released for general use.

The Randomized Controlled Trial

Randomized controlled trials (RCTs) are the most reliable way to objectively assess drug therapies. RCTs have three distinguishing features: use of controls, randomization, and blinding. All three serve to minimize the influence of personal bias on the results.

Use of Controls

When a new drug is under development, we want to know how it compares with a standard drug used for the same disorder or perhaps how it compares with no treatment at all. To make these comparisons, some subjects in the RCT are given the new drug and some are given either (1) a standard treatment or (2) a placebo (i.e., an inactive compound formulated to look like the experimental drug). Subjects receiving either the standard drug or the placebo are referred to as *controls*. Controls are important because they help us determine

TABLE 3.1 ▪ Personal Protective Equipment and Engineering Controls for Working With Hazardous Drugs in Healthcare Settings

Formulation	Activity	Double Chemotherapy Gloves	Protective Gown	Eye-Face Protection	Respiratory Protection	Ventilated Engineering Control
All types of hazardous drugs	Administration from unit-dose package	No (single glove can be used)	No	No	No	NA
Intact tablet or capsule	Cutting, crushing, or manipulating tablets or capsules; handling uncoated tablets	Yes	Yes	No	Yes, if not done in a control device	Yes[a]
Tablets or capsules	Administration	No (single glove can be used)	No	Yes, if vomit or potential to spit up[b]	No	NA
Oral liquid drug or feeding tube	Compounding	Yes	Yes	Yes, if not done in a control device	Yes, if not done in a control device	Yes[a]
	Administration	Yes	Yes	Yes, if vomit or potential to spit up[b]	No	NA
Topical drug	Compounding	Yes	Yes	Yes, if not done in a control device	Yes, if not done in a control device	Yes,[a] BSC or CACI (Note: carmustine and mustargen are volatile)
	Administration	Yes	Yes	Yes, if liquid that could splash[b]	Yes, if inhalation potential	NA
Subcutaneous/ intramuscular injection from a vial	Preparation (withdrawing from vial)	Yes	Yes	Yes, if not done in a control device	Yes, if not done in a control device	Yes, BSC or CACI
	Administration from prepared syringe	Yes	Yes	Yes, if liquid that could splash[b]	No	NA

TABLE 3.1 ▪ Personal Protective Equipment and Engineering Controls for Working With Hazardous Drugs in Healthcare Settings—cont'd

Formulation	Activity	Double Chemotherapy Gloves	Protective Gown	Eye-Face Protection	Respiratory Protection	Ventilated Engineering Control
Withdrawing and/or mixing intravenous or intramuscular solution from a vial or ampoule	Compounding	Yes[c]	Yes	No	No	Yes, BSC or CACI; use of CSTD recommended
	Administration of prepared solution	Yes	Yes	Yes; if liquid that could splash[b]	No	NA; CSTD required per USP 800 if the dosage form allows
Solution for irrigation	Compounding	Yes	Yes	Yes, if not done in a control device	Yes, if not done in a control device	Yes, BSC or CACI; use of CSTD recommended
	Administration (e.g., bladder, HIPEC, limb perfusion)	Yes	Yes	Yes	Yes	NA
Powder/solution for inhalation/ aerosol treatment	Compounding	Yes	Yes	Yes, if not done in a control device	Yes, if not done in a control device	Yes, BSC or CACI
	Aerosol administration	Yes	Yes	Yes	Yes	Yes, when applicable
	Administration	Yes	Yes	Yes, if liquid that could splash[b]	Yes, if inhalation potential	NA
Drugs and metabolites in body fluids	Disposal and cleaning	Yes	Yes	Yes, if liquid that could splash	Yes, if inhalation potential	NA
Drug-contaminated waste	Disposal and cleaning	Yes	Yes	Yes, if liquid that could splash	Yes, if inhalation potential	NA
Spills	Cleaning	Yes	Yes	Yes	Yes	NA

[a]For nonsterile preparations, a ventilated engineering control such as a fume hood or Class I BSC or a HEPA-filtered enclosure (such as a powder hood) is sufficient if the control device exhaust is HEPA filtered or appropriately exhausted to the outside of the building. It is recommended that these activities be carried out in a control device, but it is recognized that under some circumstances, this is not possible. If the activity is performed in a ventilated engineering control that is used for sterile intravenous preparations, a thorough cleaning is required after the activity.
[b]Required if patient may resist (infant, unruly patient, patient predisposed to spitting out, patient who has difficulty swallowing, veterinary patient) or if the formulation is hard to swallow.
[c]Sterile gloves are required for aseptic drug preparation in BSC or CACI.
BSC, Class II biologic safety cabinet; *CACI,* compounding aseptic containment isolator; *CSTD,* closed system drug-transfer device; *HEPA,* high-efficiency particulate air; *HIPEC,* hyperthermic intraperitoneal chemotherapy; *NA,* not applicable.
Reproduced from *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings*, 2016, pp. 32–34.

whether the new treatment is more (or less) effective than standard treatments or at least whether the new treatment is better (or worse) than no treatment at all. Likewise, controls allow us to compare the safety of the new drug with that of the old drug, a placebo, or both.

Randomization

In an RCT, subjects are randomly assigned to either the control group or the experimental group (i.e., the group receiving the new drug). The purpose of randomization is to prevent allocation bias, which results when subjects in the experimental group are different from those in the control group. For example, in the absence of randomization, researchers could load the experimental group with patients who have mild disease and load the control group with patients who have severe disease. In this case, any differences in outcome may well be because of the severity of the disease rather than differences in treatment. Moreover, even if researchers try to avoid bias by purposely assigning subjects who appear similar to both groups, allocation bias can result from *unknown* factors that can influence outcome. By assigning subjects randomly to the control and experimental groups, all factors—known and unknown, important and unimportant—should be equally represented in both groups. As a result, the influences of these

factors on outcome should tend to cancel each other out, leaving differences in the treatments as the best explanation for any differences in outcome.

Blinding

A blinded study is one in which the people involved do not know to which group—control or experimental—individual subjects have been randomized. If only the subjects have been blinded, the trial is referred to as *single blind*. If the researchers and the subjects are kept in the dark, the trial is referred to as *double blind*. Of the two, double-blind trials are more objective. Blinding is accomplished by administering the experimental drug and the control compound (either placebo or comparison drug) in identical formulations (e.g., green capsules, purple pills) that bear a numeric code. At the end of the study, the code is accessed to reveal which subjects were controls and which received the experimental drug. When subjects and researchers are not blinded, their preconceptions about the benefits and risks of the new drug can readily bias the results. Hence, blinding is done to minimize the impact of personal bias.

Stages of New Drug Development

The testing of new drugs has two principal steps: *preclinical testing* and *clinical testing*. Preclinical tests are performed in animals. Clinical tests are done in humans. The steps in drug development are shown in Table 3.2.

Preclinical Testing

Preclinical testing is required before a new drug may be tested in humans. During preclinical testing, drugs are evaluated for *toxicities, pharmacokinetic properties*, and *potentially useful biologic effects*. Preclinical tests may take 1 to 5 years. When sufficient preclinical data have been gathered, the drug developer may apply to the FDA for permission to begin testing in humans. If the application is approved, the drug is awarded *Investigational New Drug* status and clinical trials may begin.

TABLE 3.2 ■ Steps in New Drug Development

Preclinical Testing (in Animals)
- **Toxicity**
- **Pharmacokinetics**
- **Possible Useful Effects**

↓

Investigational New Drug (IND) Status

↓

Clinical Testing (in Humans)

Phase I
- *Subjects:* Healthy volunteers
- *Tests:* Metabolism, pharmacokinetics, and biologic effects

Phase II
- *Subjects:* Patients
- *Tests:* Therapeutic utility and dosage range

Phase III
- *Subjects:* Patients
- *Tests:* Safety and effectiveness

Conditional Approval of New Drug Application (NDA)

↓

Phase IV: Postmarketing Surveillance

Clinical Testing

Clinical trials occur in four phases and may take 2 to 10 years to complete. The first three phases are done before a new drug is marketed. The fourth is done after acquiring FDA approval for marketing.

Phase I. Phase I trials are usually conducted in *healthy volunteers*, but if a drug is likely to have severe side effects, as many anticancer drugs do, the trial is done in volunteer patients who have the disease under consideration. Phase I testing has three goals: to evaluate drug metabolism, pharmacokinetics, and biologic effects.

Phases II and III. In these trials, drugs are tested in *patients*. The objective is to determine therapeutic effects, dosage range, safety, and effectiveness. During Phase II and Phase III trials, 500 to 5000 patients receive the drug and only a few hundred take it for more than 3 to 6 months. After completing Phase III, the drug manufacturer applies to the FDA for conditional approval of a *New Drug Application*. If conditional approval is granted, Phase IV may begin.

Phase IV: Postmarketing Surveillance. In Phase IV, the new drug is released for general use, permitting observation of its effects in a large population. Thanks to the FDAAA of 2007, postmarketing surveillance is now much more effective than in the past.

Limitations of the Testing Procedure

It is important for nurses and other healthcare professionals to appreciate the limitations of the drug development process. Two problems are of particular concern. First, until recently, information on drug use in women and children has been limited. Second, new drugs are likely to have adverse effects that were not detected during clinical trials.

Limited Information on Women and Children

Women. Very little drug testing was done in women before 2000. In almost all cases, women of childbearing age were excluded from early clinical trials out of concern for fetal safety. Unfortunately, FDA policy took this concern to an extreme, effectively barring *all* women of childbearing age from Phase I and Phase II trials—even if the women were not pregnant and were using adequate birth control. The only women allowed to participate in early clinical trials were those with a life-threatening illness that might respond to the drug under study.

Because of limited drug testing in women, we don't know with precision how women will respond to most drugs because most drugs in current use were developed before inclusiveness of women in trials was ensured. As a result, we don't know whether beneficial effects in women will be equivalent to those seen in men, nor do we know whether adverse effects will be equivalent to those in men. We don't know how timing of drug administration with respect to the menstrual cycle will affect beneficial and adverse responses. We don't know whether drug disposition (absorption, distribution, metabolism, and excretion) will be the same in women as in men. Furthermore, of the drugs that might be used to treat a particular illness, we don't know whether the drugs that are most effective in men will also be most effective in women. Last, we don't know about the safety of drug use during pregnancy.

During the late 1990s, the FDA issued a series of guidelines mandating the participation of women (and minorities) in trials of new drugs. In addition, the FDA revoked a 1977 guideline that barred women from most trials. Because of these changes, the proportion of women in trials of most new drugs now equals the proportion of women in the population. The data generated since the implementation of the new guidelines have been reassuring: Most gender-related effects have been limited to pharmacokinetics. More importantly, for most drugs, gender has shown little impact on efficacy, safety, or dosage. Nevertheless, although the new guidelines are an important step forward, even with them, it will take a long time to close the gender gap in our knowledge of drugs.

Children. Until recently, children, like women, were excluded from clinical trials. As a result, information on dosage, therapeutic responses, and adverse effects in children has been limited. Because our knowledge of drug use in children is often derived from postmarketing surveillance, it will still be a long time before we have the information needed to use drugs safely and effectively in young patients.

Failure to Detect All Adverse Effects

Premarketing clinical trials cannot detect all adverse effects before a new drug is released. There are three reasons why: (1) During clinical trials, a relatively small number of patients are given the drug; (2) because these patients are carefully selected, they do not represent the full spectrum of individuals who will eventually take the drug; and (3) patients in trials take the drug for a relatively short time. Because of these unavoidable limitations in the testing process, effects that occur infrequently, effects that take a long time to develop, and effects that occur only in certain types of patients can go undetected. Hence, despite our best efforts, when a new drug is released, it may well have adverse effects of which we are as yet unaware. In fact, about half of the drugs that reach the market have serious adverse effects that were not detected until after they were released for general use.

The hidden dangers in new drugs are shown in Table 3.3, which presents information on eight drugs that were withdrawn from the U.S. market soon after receiving FDA approval. In all cases, the reason for withdrawal was a serious adverse effect that went undetected in clinical trials. Admittedly, only a few hidden adverse effects are as severe as the ones in the table. Hence, most do not necessitate drug withdrawal. Nonetheless, the drugs in the table should serve as a strong warning about the unknown dangers that a new drug may harbor.

Because adverse effects may go undetected, when caring for a patient who is prescribed a new drug, you should be especially watchful for previously unreported drug reactions. If a patient taking a new drug begins to show unusual symptoms, it is prudent to suspect that the new drug may be the cause—even though the symptoms are not yet mentioned in the literature.

Exercising Discretion Regarding New Drugs

When thinking about prescribing a new drug, clinicians would do well to follow this guideline: *Be neither the first to adopt the new nor the last to abandon the old*. Recall that the therapeutic objective is to produce maximum benefit with minimum harm. To achieve this objective, we must balance the potential benefits of a drug against its inherent risks. As a rule, new drugs have actions very similar to those of older agents. That is, it is rare for a new drug to be able to do something that an older drug can't accomplish. Consequently, the need to treat a particular disorder seldom constitutes a compelling reason to select a new drug over an agent that has been available for years. Furthermore, new drugs generally present greater risks than the old ones. As noted, at the time of its introduction, a new drug is likely to have adverse effects that have not yet been reported, and these effects may prove harmful for some patients. In contrast, older, more familiar drugs are less likely to cause unpleasant surprises. Consequently, when we weigh the benefits of a new drug against its risks, it is less likely that the benefits will be sufficient to justify the risks—especially when an older drug, whose properties are well known, is available. Accordingly, when it comes to the use of new drugs, it is important to be alert to the possibility that a new patient problem may be the manifestation of an as-yet-unknown adverse reaction.

TABLE 3.3 ▪ Drugs That Were Withdrawn From the U.S. Market for Safety Reasons

Drug	Indication	Year Introduced/ Year Withdrawn	Months on the Market	Reason for Withdrawal
Niacin ER/lovastatin [Advicor] Niacin ER/simvastatin [Simcor]	Hypercholesterolemia	2008/2016	96	Risks exceed benefits
Peginesatide [Omontys]	Anemia	2012/2013	12	Life-threatening reactions
Rotigotine[a] [Neupro]	Parkinson disease	2007/2008	10	Patch formulation delivered erratic doses
Tegaserod[b] [Zelnorm]	Irritable bowel syndrome	2002/2007	60	Myocardial infarction, stroke
Natalizumab[b] [Tysabri]	Multiple sclerosis	2004/2005	3	Progressive multifocal leukoencephalopathy
Rapacuronium [Raplon]	Neuromuscular blockade	1999/2001	19	Bronchospasm, unexplained fatalities
Alosetron[b] [Lotronex]	Irritable bowel syndrome	2000/2000	9	Ischemic colitis, severe constipation; deaths have occurred
Troglitazone [Rezulin]	Type 2 diabetes	1999/2000	12	Fatal liver failure

[a]Note that rotigotine was withdrawn because the *formulation* was unsafe, not because the drug itself is inherently dangerous.
[b]Alosetron, natalizumab, and tegaserod were later returned to the market. With all three drugs, risk management guidelines must be followed. Tegaserod may only be prescribed with FDA authorization for emergency situations.

DRUG NAMES

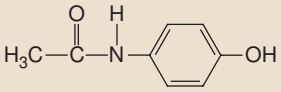
This topic is important because the names we employ affect our ability to communicate about medicines. The subject is potentially confusing because we have evolved a system in which any drug can have a large number of names.

In approaching drug names, we begin by defining the types of names that drugs have. After that, we consider (1) the complications that arise from assigning multiple names to a drug and (2) the benefits of using just one name: the generic (nonproprietary) name.

The Three Types of Drug Names

Drugs have three types of names: (1) a chemical name, (2) a generic or nonproprietary name, and (3) a brand or proprietary name (Table 3.4). All of the names in the table are for the same drug, a compound most familiar to us under the brand name *Tylenol*.

TABLE 3.4 ▪ The Three Types of Drug Names[a]



Type of Drug Name	Examples
Chemical Name	*N*-Acetyl-*para*-aminophenol
Generic Name (nonproprietary name)	Acetaminophen
Brand Names (proprietary names)	Acephen; APAP;Aspirin Free Anacin Extra Strength; Cetafen; Excedrin Tension Headache; Feverall; Little Fevers; Mapap; Nortemp Children's; Ofirmev; Pain & Fever Children's; Pain Eze; Q-Pap; RapiMed; Silapap; Triaminic; Tylenol; Valorin

[a]The chemical, generic, and brand names listed are all names for the drug whose structure is pictured in this table. This drug is most familiar to us as Tylenol, one of its brand names.

Chemical Name

The chemical name constitutes a description of a drug using the nomenclature of chemistry. As you can see from Table 3.4, a drug's chemical name can be long and complex. Because of their complexity, chemical names are inappropriate for everyday use. For example, few people would communicate using the chemical term *N*-acetyl-*para*-aminophenol when a simple generic name (*acetaminophen*) or brand name (e.g., *Tylenol*) could be used.

Generic Name

The generic name of a drug is assigned by the U.S. Adopted Names Council. Each drug has only one generic name. The generic name is also known as the *nonproprietary* name. Generic names are less complex than chemical names.

In many cases, the final syllables of the generic name indicate a drug's pharmacologic class. For example, the syllables *-cillin* at the end of *amoxicillin* indicate that amoxicillin belongs to the penicillin class of antibiotics. Similarly, the syllables *-statin* at the end of *lovastatin* indicate that lovastatin is an HMG-CoA reductase inhibitor, our most effective class of drugs for lowering cholesterol. Table 3.5 presents additional examples of generic names whose final syllables indicate the class to which the drugs belong.

Brand Name

Brand names, also known as *proprietary* or *trade* names, are the names under which a drug is marketed. These names are created by drug companies with the intention that they are easy for nurses, physicians, pharmacists, and consumers to recall and pronounce. Because any drug can be marketed in different formulations and by multiple companies, a single drug may have a large number of brand names.

Brand names must be approved by the FDA. The review process tries to ensure that no two brand names are too similar. In addition, brand names are not supposed to imply

TABLE 3.5 ▪ Generic Drug Names Whose Final Syllables Indicate Pharmacologic Class

Representative Drugs	Class-Indicating Final Syllable(s)	Pharmacologic Class	Therapeutic Use
Amoxicillin, ticarcillin	-cillin	Penicillin antibiotic	Infection
Lovastatin, simvastatin	-statin	HMG-CoA reductase inhibitor	High cholesterol
Propranolol, metoprolol	-olol	Beta-adrenergic blocker	Hypertension, angina
Phenobarbital, secobarbital	-barbital	Barbiturate	Seizures, anxiety
Benazepril, captopril	-pril	Angiotensin-converting enzyme inhibitor	Hypertension, heart failure
Candesartan, valsartan	-sartan	Angiotensin II receptor blocker	Hypertension, heart failure
Nifedipine, amlodipine	-dipine	Dihydropyridine calcium channel blocker	Hypertension
Eletriptan, sumatriptan	-triptan	Serotonin$_{1B/1D}$ receptor agonist	Migraine
Dalteparin, enoxaparin	-parin	Low-molecular-weight heparin	Anticoagulation
Sildenafil, tadalafil	-afil	Phosphodiesterase type 5 inhibitor	Erectile dysfunction
Rosiglitazone, pioglitazone	-glitazone	Thiazolidinedione	Type 2 diabetes
Omeprazole, pantoprazole	-prazole	Proton pump inhibitor	Peptic ulcer disease
Alendronate, zoledronate	-dronate	Bisphosphonate	Osteoporosis
Ciprofloxacin, norfloxacin	-floxacin	Fluoroquinolone antibiotic	Infection

efficacy—which may be why orlistat (a diet pill) is named *Xenical*, rather than something more suggestive, like *Fat-B-Gone* or *PoundsOff*. Nevertheless, despite the rule against suggestive names, some still slip by FDA scrutiny, like these two gems: *Flomax* (tamsulosin) and *Rapaflo* (silodosin). Can you guess what these drugs are used for? (Hint: It's an old guy malady.)

Which Name to Use, Generic or Brand?

Just as scientists use a common terminology to discuss scientific phenomena, we need common terminology when discussing drugs. When large numbers of drug names are unfamiliar or not standardized, as is common with many brand names, it creates the potential for confusion. For this reason, many professionals advocate for the universal use of generic names.

Problems With Brand Names

A Single Drug Can Have Multiple Brand Names. The principal objection to brand names is their vast number. Although a drug can have only one generic name, it can have unlimited brand names. As the number of brand names for a single drug expands, the burden of name recognition becomes progressively heavier. By way of illustration, the drug whose generic name is acetaminophen has more than 15 brand names (see Table 3.4). Although most clinicians will recognize this drug's generic name, few are familiar with all the brand names.

The use of brand names can result in medication overdosage with potentially disastrous results. Because patients frequently see more than one healthcare provider, a patient may receive prescriptions for the same drug by two (or more) prescribers. If the provider refers to these drugs by their brand names, the patient may believe these are two different drugs. If these medications are taken as prescribed, excessive dosing will result.

Over-the-Counter Products With the Same Brand Name May Have Different Active Ingredients. As indicated in Table 3.6, OTC products that have similar or identical brand names can actually contain different drugs. For example, although the two Lotrimin AF products have identical brand names, they actually contain two different drugs: miconazole and clotrimazole. Confusion would be avoided by labeling these products *miconazole spray* and *clotrimazole cream*, rather than labeling both Lotrimin AF.

The two 4-Way Nasal Spray products listed in Table 3.6 further illustrate the potential for confusion. For most drugs, the words "fast-acting" and "long-acting" indicate different formulations of the same drug; however, 4-Way Fast-Acting Nasal Spray is phenylephrine and 4-Way 12-Hour Nasal Spray is oxymetazoline.

Perhaps the most disturbing aspect of brand names is illustrated by the reformulation of *Kaopectate*, a well-known antidiarrheal product. In 2003, the manufacturer switched the active ingredient in Kaopectate from attapulgite (which had replaced kaolin and pectin in the late 1980s) to bismuth subsalicylate. Nevertheless, although the active ingredient changed, the brand name did not. As a result, current formulations of Kaopectate pose a risk for patients who should not take salicylates, such as young children at risk for Reye's syndrome. This example illustrates an important point: Manufacturers of OTC drugs can reformulate brand-name products whenever they want—without changing the name at all. Hence, there is no guarantee that the brand-name product you buy today contains the same drug as the brand-name product you bought last week, last month, or last year.

TABLE 3.6 ▪ Some OTC Products That Share the Same Brand Name

Product Name	Drugs in the Product
Lotrimin AF	Miconazole (spray)
Lotrimin AF	Clotrimazole (cream)
4-Way 12-Hour Nasal Spray	Oxymetazoline
4-Way Fast-Acting Nasal Spray	Phenylephrine
Kaopectate	Originally formulated as *kaolin + pectin* Reformulated to *attapulgite* in the late 1980s Reformulated to *bismuth subsalicylate* in 2003

OTC, Over-the-counter.

In the spring of 1999, the FDA issued a ruling to help reduce the confusion created by OTC brand names. This ruling requires generic names for the drugs in OTC products to be clearly and prominently listed on the label. Unfortunately, this is of no help to patients who have long relied on brand names alone to guide OTC choices.

Brand Names Can Endanger International Travelers. For people who travel to other countries, brand names present two kinds of problems. First, the brand name used in one country may differ from the brand name used in another country. The second (and more disturbing) problem is this: Products with the *identical* brand names may have *different* active ingredients, depending on where you buy the drug (Table 3.7). As a result, when a prescription for a brand-name product is filled in another country, the patient may receive the wrong drug. For example, when visiting Mexico, Americans or Canadians with a prescription for *Vantin* will be given naproxen (an antiinflammatory drug) rather than the cefpodoxime (an antibiotic) that they were expecting. Not only can this lead to unnecessary side effects (possible kidney damage and gastrointestinal ulceration), but the target infection will continue unabated. Hence, the patient is exposed to all the risks of medication without getting any of the benefits.

Generic Products Versus Brand-Name Products

To complete our discussion of drug names, we need to address two questions: (1) Do significant differences exist between different brands of the same drug? And (2) if such differences do exist, do they justify the use of brand names? The answer to both questions is NO!

Are Generic Products and Brand-Name Products Therapeutically Equivalent? When a new drug comes to market, it is sold under a brand name by the company that developed it. When that company's patent expires, other companies can produce the drug and market it under its generic name. (A list of FDA-approved generic equivalents is available online at www.accessdata.fda.gov/scripts/cder/ob/default.cfm.) Our question, then, is, "Are the generic formulations equivalent to the brand-name formulation produced by the original manufacturer?"

Because all equivalent products—generic or brand name—contain the same dose of the same drug, the only real concern with generic formulations is their rate and extent of absorption. For a few drugs, a slight increase in absorption can result in toxicity, and a slight decrease can result in therapeutic failure. For example, when health plans in Minnesota required

TABLE 3.7 ■ Products From the United States and Canada That Have the Same Brand Name but Different Active Ingredients in Other Countries

Brand Name	Country	Active Drug	Indication
Norpramin	United States, Canada	Desipramine	Depression
	Spain	Omeprazole	Peptic ulcer disease
Flomax	United States, Canada	Tamsulosin	Enlarged prostate
	Italy	Morniflumate	Inflammation
Allegra	United States, Canada	Fexofenadine	Allergies
	Germany	Frovatriptan	Migraine
Mobic	United States, Canada	Meloxicam	Inflammation, pain
	India	Amoxicillin	Bacterial infection
Avastin	United States, Canada	Bevacizumab	Cancer, macular degeneration
	India	Atorvastatin	High cholesterol
Vantin	United States, Canada	Cefpodoxime	Bacterial infection
	Mexico	Naproxen	Inflammation, pain

the substitution of generic for brand-name drugs, patients at MINCEP Epilepsy Care whose symptoms were previously controlled with Dilantin (phenytoin) began to have seizures after switching to a generic form of phenytoin. Hence, with agents for which a small difference in absorption can be important, decisions to stay with a brand name should be based on the evidence and made on a case-by-case basis.

Conclusions Regarding Generic Names and Brand Names

In the preceding discussion, we considered concerns associated with brand names and generic names. In this text, generic names are employed for routine discussion. Although brand names are presented, they are not emphasized.

OVER-THE-COUNTER DRUGS

OTC drugs are defined as drugs that can be purchased without a prescription. These agents are used for a wide variety of complaints, including mild pain, motion sickness, allergies, colds, constipation, and heartburn. Whether a drug is available by prescription or over the counter is ultimately determined by the FDA.

OTC drugs are an important part of healthcare. When used properly, these agents can provide relief from many ailments, while saving consumers the expense and inconvenience of visiting a prescriber. The following facts underscore how important the OTC market is:

- Americans spend more than $30 billion annually on OTC drugs.
- OTC drugs account for 60% of all medications administered.
- Forty percent of Americans take at least one OTC drug every 2 days.
- Four times as many illnesses are treated by a consumer using an OTC drug as by a consumer visiting a prescriber.
- With most illnesses (60%–95%), initial therapy consists of self-care, including self-medication with an OTC drug.
- The average home medicine cabinet contains 24 OTC preparations.

Some drugs that were originally sold only by prescription are now sold over the counter. Since the 1970s, more than 100 prescription drugs have been switched to OTC status. Because of this process, more and more highly effective drugs are becoming directly available to consumers. Unfortunately, most consumers lack the knowledge needed to choose the most appropriate drug from among the steadily increasing options.

In 2006, the FDA began to phase in new labeling requirements for OTC drugs. The goal is to standardize labels and to make them more informative and easy to understand. The labels, titled *Drug Facts*, are to be written in plain language, have a user-friendly format, and use type that is big enough to read. Active ingredients will be listed first, followed by uses, warnings, directions, and inactive ingredients. This information is designed to help consumers select drugs that can provide the most benefit with the least risk.

In contrast to some texts, which present all OTC drugs in a single chapter, this text presents OTC drugs throughout. This format allows discussion of OTC drugs in their proper pharmacologic and therapeutic contexts.

SOURCES OF DRUG INFORMATION

There is much more to pharmacology than we can address in this text. When you need additional information, the following sources may be helpful.

Newsletters

The Medical Letter on Drugs and Therapeutics is a bimonthly publication that provides drug information and updates. A typical issue addresses two or three agents. Discussions consist of a summary of data from clinical trials plus a conclusion regarding the drug's therapeutic utility. Comparative drug reviews for specific drug indications add additional guidance for deciding whether a new drug is an appropriate choice. This newsletter is available both in print and online. Subscribing information is available at https://secure.medicalletter.org/subTML.

Nurse's Letter is available as an online component of *Prescriber's Letter*, which is a monthly publication that provides

the latest information regarding drug therapy. This newsletter summarizes major drug-related developments—from new drugs to FDA warnings to new uses of older agents. Resources such as toolboxes and well-organized charts are offered. It is available in both print and online versions. Free continuing education is offered. Subscribing information is available at https://prescriber.therapeuticresearch.com/Home/PRL.

Reference Books

The *Physicians' Desk Reference*, also known as the PDR, is a reference work financed by the pharmaceutical industry. The information on each drug is identical to the FDA-approved information on its package insert. In addition to textual content, the PDR has a pictorial section for product identification. The PDR is updated annually and is available online.

Drug Facts and Comparisons is a comprehensive reference that contains monographs on virtually every drug marketed in the United States. Information is provided on drug actions, indications, warnings, precautions, adverse reactions, dosage, and administration. In addition to describing the properties of single medications, the book lists the contents of most combination products sold in this country. Indexing is by generic name and brand name. *Drug Facts and Comparisons* is available in a loose-leaf format (updated monthly), an online format (updated monthly), and a hard-cover format (published annually).

A number of drug references have been compiled expressly for nurses. All address topics of special interest to nurses, including information on administration, assessment, evaluation, and patient education. Representative nursing drug references include *Saunders Nursing Drug Handbook* and *Mosby's Nursing Drug Reference*, both published annually.

The Internet

The Internet can be a valuable source of drug information, but finding reliable and authoritative drug information online can be a challenge! Accordingly, you need to exercise discretion when searching for information.

DailyMed is a U.S. government website that provides FDA-approved drug labeling (package inserts) for both generic and brand name drugs. As labeling is changed, information is updated so that it remains current, unlike many of the popular drug information sites that post information once and leave it there even after drugs are removed from the market. This searchable database is available at https://dailymed.nlm.nih.gov/dailymed/index.cfm.

If you cannot find the drug you seek at DailyMed, it may have been discontinued by the manufacturer or otherwise removed from the market. You can check the status by going to http://www.accessdata.fda.gov/scripts/cder/drugsatfda to see if a drug or particular formulation of a drug has been discontinued.

Finally, the Prescriber's Digital Reference offers summaries of drug information and drug alerts online. The searchable database is located at https://www.pdr.net/browse-by-drug-name.

KEY POINTS

- The Food, Drug, and Cosmetic Act of 1938 was the first legislation to regulate drug safety.
- The Harris-Kefauver Amendments, passed in 1962, were the first legislation to demand that drugs actually be of some benefit.
- The Controlled Substances Act, passed in 1970, set rules for the manufacture and distribution of drugs considered to have potential for abuse.
- The FDA Amendments Act, passed in 2007, expanded the mission of the FDA to include rigorous oversight of drug safety *after* a drug has been released for marketing.
- The Comprehensive Addiction and Recovery Act of 2016 provides funding to combat a nationwide opioid epidemic by addressing the crisis from multiple approaches.
- The National Institute for Occupational Safety and Health (NIOSH) identifies drugs that are hazardous for handling and provides instructions for use of protective equipment and environmental controls to protect nurses and other healthcare workers from harm resulting from exposure.
- Development of a new drug is a very expensive process that takes years to complete.
- The randomized controlled trial is the most reliable way to objectively assess drug efficacy and safety.
- Clinical trials occur in four phases. The first three phases are done before a new drug is marketed. The fourth is done after FDA approval for marketing.
- Drug testing in Phase II and Phase III clinical trials is limited to a relatively small number of patients, most of whom take the drug for a relatively short time.
- Because women and children have been excluded from drug trials in the past, our understanding of drug efficacy and safety in these groups is limited for many drugs.
- When a new drug is released for general use, it may well have adverse effects that have not yet been detected. Consequently, when working with a new drug, you should be especially watchful for previously unreported adverse events.
- Drugs have three types of names: a chemical name, a generic or nonproprietary name, and a brand or proprietary name.
- Each drug has only one generic name but can have many brand names.
- With over-the-counter (OTC) products, the same brand name may be used for more than one drug.
- Brand names for the same drug may differ from one country to another.
- Generic names facilitate communication better than brand names, which are potentially confusing.
- OTC drugs are drugs that can be purchased without a prescription.

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UNIT II

BASIC PRINCIPLES OF PHARMACOLOGY

CHAPTER 4

Pharmacokinetics

The term *pharmacokinetics* is derived from two Greek words: *pharmakon* (drug or poison) and *kinesis* (motion). As this derivation implies, pharmacokinetics is the study of drug movement throughout the body. Pharmacokinetics also includes what happens to the drug as it makes this journey.

There are four basic pharmacokinetic processes: *absorption, distribution, metabolism*, and *excretion* (Fig. 4.1). Absorption is the drug's movement from its site of administration into the blood. Distribution is the drug's movement from the blood to the interstitial space of tissues and from there into cells. Metabolism (biotransformation) is the enzymatically mediated alteration of drug structure. Excretion is the movement of drugs and their metabolites out of the body. The combination of metabolism plus excretion is called *elimination*. The four pharmacokinetic processes, acting in concert, determine the concentration of a drug at its sites of action.

APPLICATION OF PHARMACOKINETICS IN THERAPEUTICS

By applying knowledge of pharmacokinetics to drug therapy, we can help maximize beneficial effects and minimize harm. Recall that the intensity of the response to a drug is directly related to the concentration of the drug at its site of action. To maximize beneficial effects, a drug must achieve concentrations that are high enough to elicit desired responses; to minimize harm, we must avoid concentrations that are too high. This balance is achieved by selecting the most appropriate route, dosage, and dosing schedule.

As a nurse, you will have ample opportunity to apply knowledge of pharmacokinetics in clinical practice. For example, by understanding the reasons behind selection of route, dosage, and dosing schedule, you will be less likely to commit medication errors than will the nurse who, through lack of this knowledge, administers medications by blindly following prescribers' orders. Also, as noted in Chapter 2, prescribers do make mistakes. Accordingly, you will have occasion to question or even challenge prescribers regarding their selection of dosage, route, or schedule of administration. To alter a prescriber's decision, you will need logical rationale to support your position. To present your case, you will need to understand pharmacokinetics.

Knowledge of pharmacokinetics can increase job satisfaction. Working with medications is a significant component of nursing practice. If you lack knowledge of pharmacokinetics, drugs will always be somewhat mysterious and, as a result, will be a potential source of unease. By helping to demystify drug therapy, knowledge of pharmacokinetics can decrease some of the stress of nursing practice and can increase intellectual and professional satisfaction.

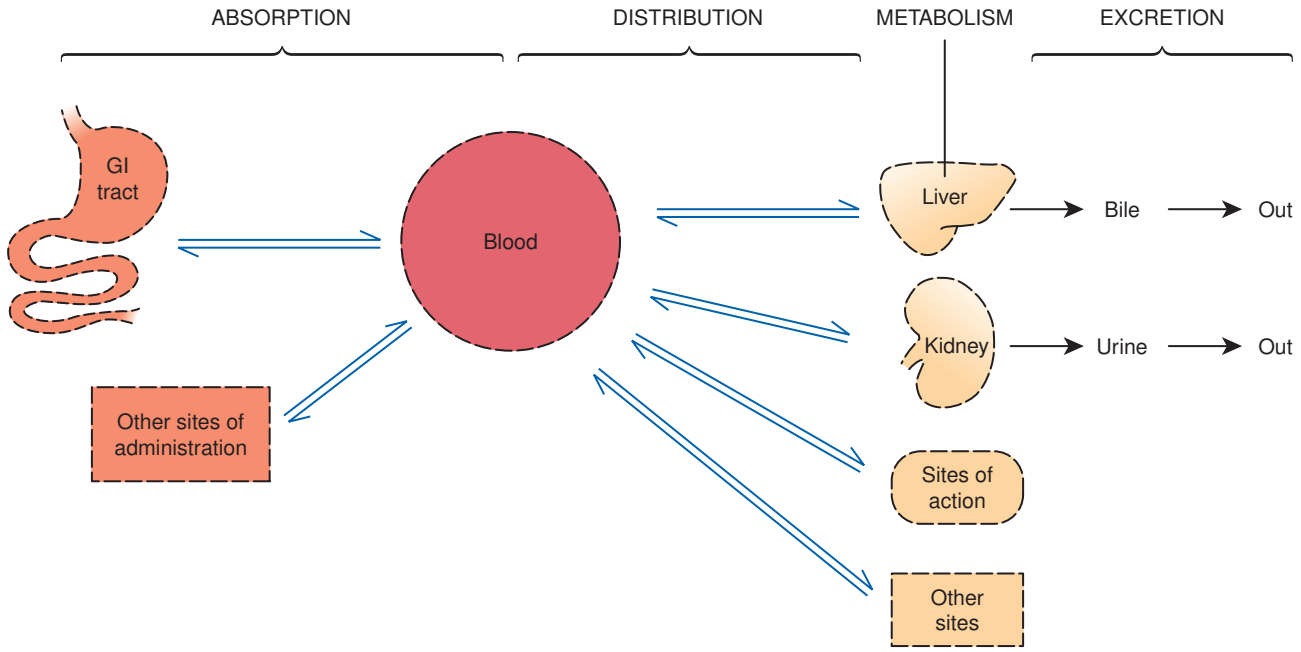

Fig. 4.1 ▪ The four basic pharmacokinetic processes.
Dotted lines represent membranes that must be crossed as drugs move throughout the body. *GI,* Gastrointestinal.

A NOTE TO CHEMOPHOBES

Before we proceed, some advance notice (and encouragement) is in order for chemophobes (students who fear chemistry). Because drugs are chemicals, we cannot discuss pharmacology meaningfully without occasionally talking about chemistry. This chapter has some chemistry in it. Because the concepts addressed here are fundamental, and because they reappear frequently, all students, including chemophobes, are encouraged to learn this material now, regardless of the effort and anxiety involved.

I also want to comment on the chemical structures that appear in the book. Structures are presented only to illustrate and emphasize concepts. They are not intended for memorization, and they are certainly not intended for exams. So, relax, look at the pictures, and focus on the concepts.

PASSAGE OF DRUGS ACROSS MEMBRANES

All four phases of pharmacokinetics—absorption, distribution, metabolism, and excretion—involve drug movement. To move throughout the body, drugs must cross membranes. Drugs must cross membranes to enter the blood from their site of administration. Once in the blood, drugs must cross membranes to leave the vascular system and reach their sites of action. In addition, drugs must cross membranes to undergo metabolism and excretion. Accordingly, the factors that determine the passage of drugs across biologic membranes have a profound influence on all aspects of pharmacokinetics.

Membrane Structure

Biologic membranes are composed of layers of individual cells. The cells composing most membranes are very close to one another—so close, in fact, that drugs must usually pass *through* cells, rather than between them, to cross the membrane. Hence, the ability of a drug to cross a biologic membrane is determined primarily by its ability to pass through single cells. The major barrier to passage through a cell is the cytoplasmic membrane (the membrane that surrounds every cell).

The basic structure of the cell membrane is depicted in Fig. 4.2. As indicated, the membrane structure consists of a double layer of molecules known as *phospholipids*. Phospholipids are simply lipids (fats) that contain an atom of phosphate.

In Fig. 4.2, the phospholipid molecules are depicted as having a round head (the phosphate-containing component) and two tails (long-chain hydrocarbons). The large objects embedded in the membrane represent protein molecules, which serve a variety of functions.

Three Ways to Cross a Cell Membrane

The three most important ways by which drugs cross cell membranes are (1) passage through channels or pores, (2) passage with the aid of a transport system, and (3) direct penetration of the membrane itself. Of the three, direct penetration of the membrane is most common.

Channels and Pores

Very few drugs cross membranes via channels or pores. The channels in membranes are extremely small (approximately 4 angstroms or less), and are specific for certain molecules. Consequently, only the smallest of compounds (e.g., potassium or sodium) can pass through these channels, and then only if the channel is the right one.

Transport Systems

Transport systems are carriers that can move drugs from one side of the cell membrane to the other. Some transport systems

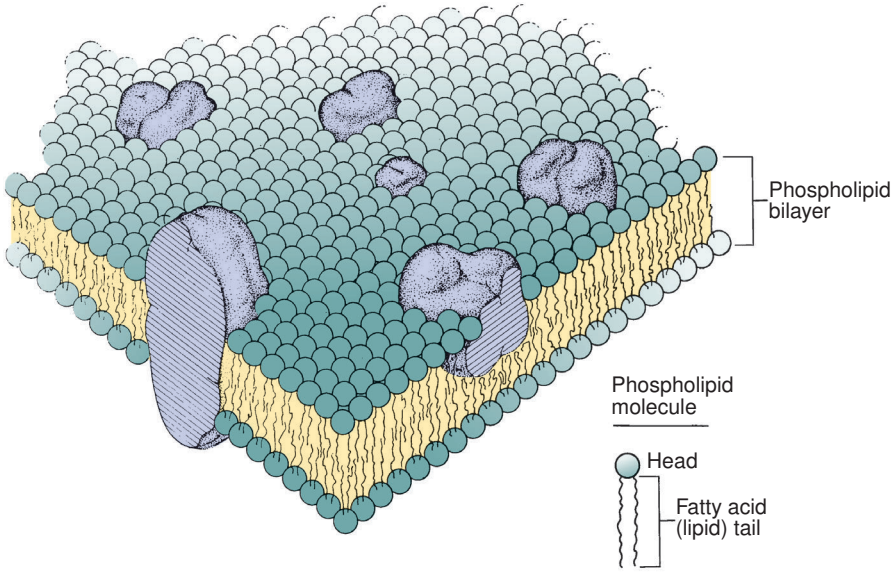

Fig. 4.2 ■ Structure of the cell membrane.
The cell membrane consists primarily of a double layer of phospholipid molecules. The large globular structures represent protein molecules embedded in the lipid bilayer. (Modified from Singer SJ, Nicolson GL. The fluid mosaic model of the structure of cell membranes. *Science.* 1972; 175:72.)

require the expenditure of energy; others do not. All transport systems are selective and will not carry just any drug. Whether a transporter will carry a particular drug depends on the drug's structure.

Transport systems are an important means of drug transit. For example, certain orally administered drugs could not be absorbed unless there were transport systems to move them across the membranes that separate the lumen of the intestine from the blood. A number of drugs could not reach intracellular sites of action without a transport system to move them across the cell membrane. Renal excretion of many drugs would be extremely slow were it not for transport systems in the kidney that can pump drugs from the blood into the renal tubules.

P-Glycoprotein. One transporter, known as *P-glycoprotein (PGP)* or *multidrug transporter protein*, deserves special mention. PGP is a transmembrane protein that transports a wide variety of drugs *out* of cells. This transporter is present in cells at many sites, including the liver, kidney, placenta, intestine, and capillaries of the brain. In the liver, PGP transports drugs into the bile for elimination. In the kidney, it pumps drugs into the urine for excretion. In the placenta, it transports drugs back into the maternal blood, thereby reducing fetal drug exposure. In the intestine, it transports drugs into the intestinal lumen and can thereby reduce drug absorption into the blood. Finally, in brain capillaries, it pumps drugs into the blood, thereby limiting drug access to the brain.

Direct Penetration of the Membrane

For most drugs, movement throughout the body is dependent on the ability to penetrate membranes directly. Why? Because (1) most drugs are too large to pass through channels or pores, and (2) most drugs lack transport systems to help them cross all of the membranes that separate them from their sites of action, metabolism, and excretion.

A general rule in chemistry states that "like dissolves like." Membranes are composed primarily of lipids; therefore to directly penetrate membranes, a drug must be *lipid soluble* (lipophilic).

Certain kinds of molecules are *not* lipid soluble and therefore cannot penetrate membranes. This group consists of *polar molecules* and *ions*.

Polar Molecules. Polar molecules are molecules with an uneven distribution of electrical charge. That is, positive and negative charges within the molecule tend to congregate separately from one another. Water is the classic example. As depicted in Fig. 4.3A, the electrons (negative charges) in the water molecule spend more time in the vicinity of the oxygen atom than in the vicinity of the two hydrogen atoms. As a result, the area around the oxygen atom tends to be negatively charged, whereas the area around the hydrogen atoms tends to be positively charged. Gentamicin (see Fig. 4.3B), an antibiotic, is an example of a polar drug. The hydroxyl groups, which attract electrons, give gentamicin its polar nature.

Although polar molecules have an uneven *distribution* of charge, they have no *net* charge. Polar molecules have an equal number of protons (which bear a single positive charge) and electrons (which bear a single negative charge). As a result, the positive and negative charges balance each other exactly, and the molecule as a whole has neither a net positive charge nor a net negative charge. Molecules that *do* bear a net charge are called *ions*. These are discussed in the following section.

In accord with the "like dissolves like" rule, polar molecules will dissolve in *polar* solvents (such as water) but not in *nonpolar* solvents (such as oil). Table sugar provides a common example. Sugar, a polar compound, readily dissolves in water but not in salad oil, butter, and other lipids, which are nonpolar compounds. Just as sugar is unable to dissolve in lipids, polar drugs are unable to dissolve in the lipid bilayer of the cell membrane.

Ions. Ions are defined as molecules that have a *net electrical charge* (either positive or negative). Except for very small molecules, *ions are unable to cross membranes.*

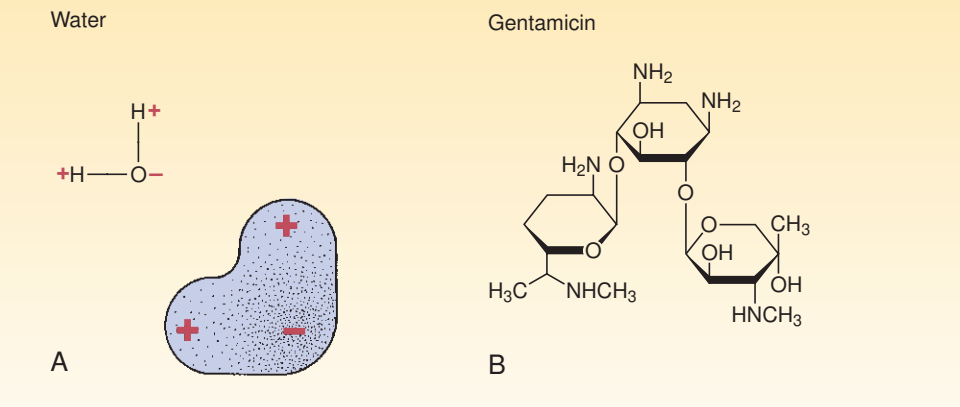

Fig. 4.3 ■ **Polar molecules.**
A, Stippling shows the distribution of electrons within the water molecule. As indicated at the lower right, water's electrons spend more time near the oxygen atom than near the hydrogen atoms, making the area near the oxygen atom somewhat negative and the area near the hydrogen atoms more positive. **B,** Gentamicin is a polar drug. The two –OH groups of gentamicin attract electrons, thereby causing the area around these groups to be more negative than the rest of the molecule.

Quaternary Ammonium Compounds

Quaternary ammonium compounds are molecules that contain at least one atom of nitrogen and *carry a positive charge at all times*. The constant charge on these compounds results from atypical bonding to the nitrogen. In most nitrogen-containing compounds, the nitrogen atom bears only three chemical bonds. In contrast, the nitrogen atoms of quaternary ammonium compounds have four chemical bonds. Because of the fourth bond, quaternary ammonium compounds always carry a positive charge. Moreover, because of the charge, these compounds are unable to cross most membranes.

Tubocurarine is a representative quaternary ammonium compound. Until recently, purified tubocurarine was employed as a muscle relaxant for surgery and other procedures. A crude preparation—curare—is used by South American Indians as an arrow poison. When employed for hunting, tubocurarine (curare) produces paralysis of the diaphragm and other skeletal muscles, causing death by asphyxiation. Interestingly, even though meat from animals killed with curare is laden with poison, it can be eaten with no ill effect. Why? Because tubocurarine, being a quaternary ammonium compound, cannot cross membranes, and therefore cannot be absorbed from the intestine; as long as it remains in the lumen of the intestine, curare can do no harm. As you might gather, when tubocurarine was used clinically, it could not be administered by mouth. Instead, it had to be injected. Once in the bloodstream, tubocurarine then had ready access to its sites of action on the surface of muscles.

pH-Dependent Ionization

Unlike quaternary ammonium compounds, which always carry a charge, many drugs are either weak organic acids or weak organic bases, which can exist in charged and uncharged forms. Whether a weak acid or base carries a charge is determined by the pH of the surrounding medium.

A review of acid-base chemistry should help. An acid is defined as a compound that can give up a hydrogen ion (proton). Put another way, *an acid is a proton donor*. A base is defined as a compound that can take on a hydrogen ion. That is, *a base is a proton acceptor*. When an acid gives up its proton, which is positively charged, the acid itself becomes negatively charged. Conversely, when a base accepts a proton, the base becomes positively charged. These reactions are depicted in Fig. 4.4, which shows aspirin as a representative acid and amphetamine as a representative base. Because the process of an acid giving up a proton or a base accepting a proton converts the acid or base into a charged particle (ion), the process for either an acid or a base is termed *ionization*.

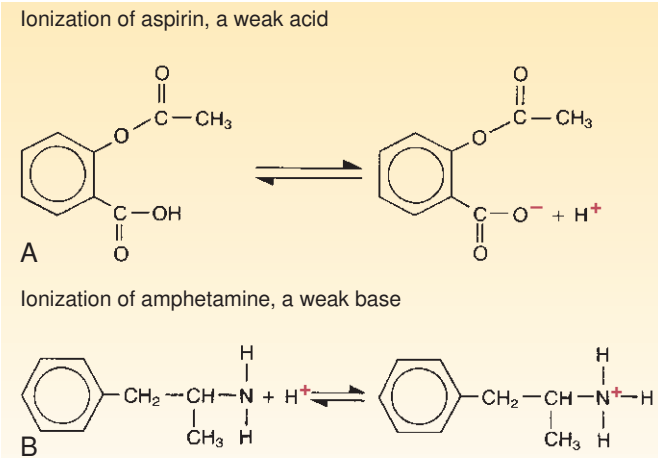

Fig. 4.4 ■ **Ionization of weak acids and weak bases.**
The extent of ionization of weak acids (**A**) and weak bases (**B**) depends on the pH of their surroundings. The ionized (charged) forms of acids and bases are not lipid soluble and hence do not readily cross membranes. Note that acids ionize by giving up a proton, and that bases ionize by taking on a proton.

The extent to which a weak acid or weak base becomes ionized is determined in part by the pH of its environment. The following rules apply:

- Acids tend to ionize in basic (alkaline) media.
- Bases tend to ionize in acidic media.

To illustrate the importance of pH-dependent ionization, consider the ionization of aspirin. Aspirin, an acid, tends to give up its proton (become ionized) in basic media.

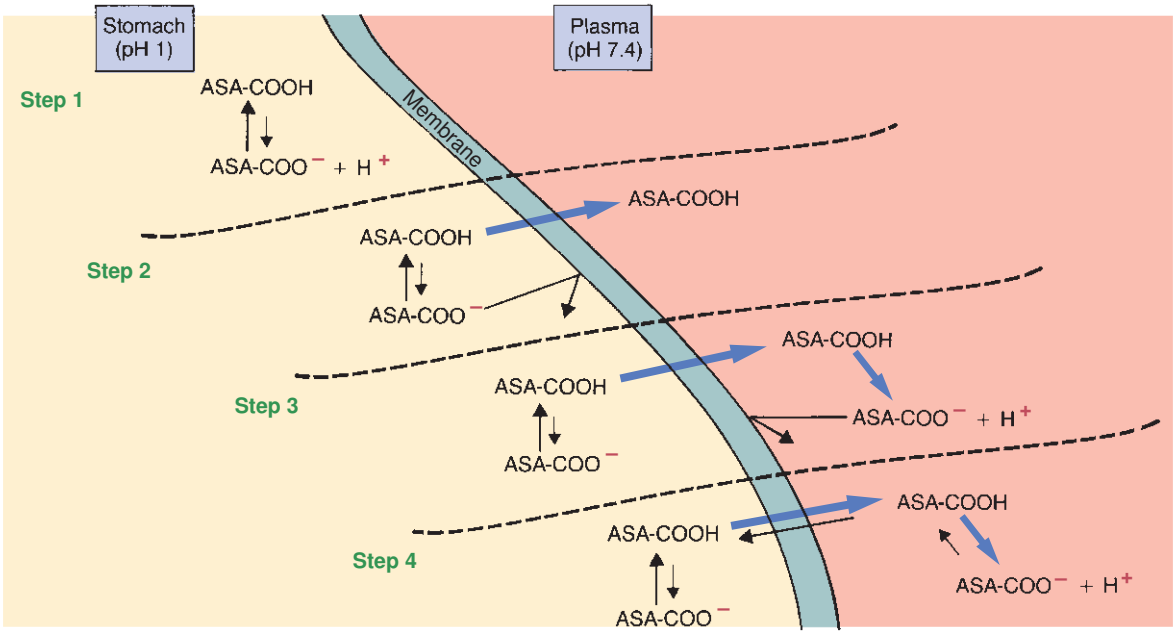

Fig. 4.5 ■ **Ion trapping of drugs.**
This figure demonstrates ion trapping using aspirin as an example. Because aspirin is an acidic drug, it will be nonionized in acid media and ionized in alkaline media. As indicated, ion trapping causes molecules of orally administered aspirin to move from the acidic (pH 1) environment of the stomach to the more alkaline (pH 7.4) environment of the plasma, thereby causing aspirin to accumulate in the blood. In the figure, aspirin (acetylsalicylic acid) is depicted as ASA with its COOH (carboxylic acid) group attached. ***Step 1:*** Once ingested, ASA dissolves in the stomach contents, after which some ASA molecules give up a proton and become ionized. Nevertheless, most of the ASA in the stomach remains nonionized because the stomach is acidic, and acidic drugs do not ionize in acidic media. ***Step 2:*** Because most ASA molecules in the stomach are nonionized (and therefore lipid soluble), most ASA molecules in the stomach can readily cross the membranes that separate the stomach lumen from the plasma. Because of the concentration gradient that exists between the stomach and the plasma, nonionized ASA molecules will begin moving into the plasma. (Note that, because of their charge, ionized ASA molecules cannot leave the stomach.) ***Step 3:*** As the nonionized ASA molecules enter the relatively alkaline environment of the plasma, most give up a proton (H^+) and become negatively charged ions. ASA molecules that become ionized in the plasma cannot diffuse back into the stomach. ***Step 4:*** As the nonionized ASA molecules in the plasma become ionized, more nonionized molecules will pass from the stomach to the plasma to replace them. This movement occurs because the laws of diffusion demand equal concentrations of diffusible substances on both sides of a membrane. Because only the nonionized form of ASA is able to diffuse across the membrane, it is this form that the laws of diffusion will attempt to equilibrate. Nonionized ASA will continue to move from the stomach to the plasma until the amount of ionized ASA in plasma has become large enough to prevent conversion of newly arrived nonionized molecules into the ionized form. Equilibrium will then be established between the plasma and the stomach. At equilibrium, there will be equal amounts of *nonionized* ASA in the stomach and plasma. On the plasma side, however, the amount of ionized ASA will be much larger than on the stomach side. Because there are equal concentrations of nonionized ASA on both sides of the membrane, but a much higher concentration of ionized ASA in the plasma, the total concentration of ASA in plasma will be much higher than that in the stomach.

Conversely, aspirin keeps its proton and remains nonionized in acidic media. Accordingly, when aspirin is in the stomach (an acidic environment), most of the aspirin molecules remain nonionized. Because aspirin molecules are nonionized in the stomach, they can be absorbed across the membranes that separate the stomach from the bloodstream. When aspirin molecules pass from the stomach into the small intestine, where the environment is relatively alkaline, they change to their ionized form. As a result, absorption of aspirin from the intestine is impeded.

pH Partitioning (Ion Trapping)

Because the ionization of drugs is pH dependent, when the pH of the fluid on one side of a membrane differs from the pH of the fluid on the other side, drug molecules will tend to accumulate on the side where the pH most favors their ionization. Accordingly, because acidic drugs tend to ionize in basic media and because basic drugs tend to ionize in acidic media, *when there is a pH gradient between two sides of a membrane:*

- Acidic drugs will accumulate on the alkaline side.
- Basic drugs will accumulate on the acidic side.

The process whereby a drug accumulates on the side of a membrane where the pH most favors its ionization is referred to as *ion trapping* or *pH partitioning*. Fig. 4.5 shows the steps of ion trapping using aspirin as an example.

Because ion trapping can influence the movement of drugs throughout the body, the process is not simply of academic interest. Rather, ion trapping has practical clinical implications. Knowledge of ion trapping helps us understand drug absorption, as well as the movement of drugs to sites of action, metabolism, and excretion. An understanding of ion trapping

can be put to practical use when we need to actively influence drug movement. Poisoning is the principal example: By manipulating urinary pH, we can employ ion trapping to draw toxic substances from the blood into the urine, thereby accelerating their removal.

ABSORPTION

Absorption is defined as *the movement of a drug from its site of administration into the blood*. The *rate* of absorption determines how *soon* effects will begin. The *amount* of absorption helps determine how *intense* effects will be.

Factors Affecting Drug Absorption

The rate at which a drug undergoes absorption is influenced by the physical and chemical properties of the drug itself and by physiologic and anatomic factors at the absorption site.

Rate of Dissolution

Before a drug can be absorbed, it must first dissolve. Hence, the rate of dissolution helps determine the rate of absorption. Drugs in formulations that allow rapid dissolution have a faster onset than drugs formulated for slow dissolution.

Surface Area

The surface area available for absorption is a major determinant of the rate of absorption. The larger the surface area, the faster absorption will be. For this reason, orally administered drugs are usually absorbed from the small intestine rather than from the stomach. (Recall that the small intestine, because of its lining of microvilli, has an extremely large surface area, whereas the surface area of the stomach is relatively small.)

Blood Flow

Drugs are absorbed most rapidly from sites where blood flow is high. Why? Because blood containing a newly absorbed drug will be replaced rapidly by drug-free blood, thereby maintaining a large gradient between the concentration of drug outside the blood and the concentration of drug in the blood. The greater the concentration gradient, the more rapid absorption will be.

Lipid Solubility

As a rule, highly lipid-soluble drugs are absorbed more rapidly than drugs whose lipid solubility is low. Why? Because lipid-soluble drugs can readily cross the membranes that separate them from the blood, whereas drugs of low lipid solubility cannot.

pH Partitioning

pH partitioning can influence drug absorption. Absorption is enhanced when the difference between the pH of plasma and the pH at the site of administration is such that drug molecules have a greater tendency to be ionized in the plasma.

Characteristics of Commonly Used Routes of Administration

The routes of administration that are used most commonly fall into two major groups: *enteral* (via the gastrointestinal [GI] tract) and *parenteral*. The literal definition of *parenteral* is *outside the GI tract*. In common parlance, however, the term *parenteral* is used to mean *by injection*. The principal parenteral routes are *intravenous, subcutaneous*, and *intramuscular*.

For each of the major routes of administration—oral (PO), intravenous (IV), intramuscular (IM), and subcutaneous (subQ)—the pattern of drug absorption (i.e., the rate and extent of absorption) is unique. Consequently, the route by which a drug is administered will significantly affect both the onset and the intensity of effects. Why do patterns of absorption differ between routes? Because the barriers to absorption associated with each route are different. In the discussion that follows, we examine these barriers and their influence on absorption pattern. In addition, as we discuss each major route, we will consider its clinical advantages and disadvantages. The distinguishing characteristics of the four major routes are summarized in Table 4.1.

Intravenous

Barriers to Absorption. When a drug is IV administered, there are no barriers to absorption. Why? Because, with IV administration, absorption is bypassed. Recall that absorption is defined as the movement of a drug from its site of administration into the blood. Because IV administration puts a drug directly into the bloodstream, all barriers are bypassed.

Absorption Pattern. IV administration results in absorption that is both instantaneous and complete. Absorption is instantaneous in that drug enters the blood directly. Absorption is complete in that virtually all of the administered dose reaches the blood.

Advantages

Rapid Onset. Intravenous administration results in rapid onset of action. Although rapid onset is not always important, it has an obvious benefit in emergencies.

Control. Because the entire dose is administered directly into the blood, the nurse has precise control over levels of drug in the blood. This contrasts with the other major routes of administration, and especially with oral administration, in which the amount absorbed is less predictable.

Permits Use of Large Fluid Volumes. The IV route is the only parenteral route that permits the use of large volumes of fluid. Some drugs that require parenteral administration are poorly soluble in water and hence must be dissolved in a large volume. Because of the physical limitations presented by soft tissues (e.g., muscle, subcutaneous tissue), injection of large volumes at these sites is not feasible. In contrast, the amount of fluid that can be infused into a vein, although limited, is nonetheless relatively large.

Permits Use of Irritant Drugs. Certain drugs, because of their irritant properties, can only be IV administered. A number of anticancer drugs, for example, are very chemically reactive. If present in high concentrations, these agents can cause severe local injury. When administered through a freely flowing IV line, however, these drugs are rapidly diluted in the blood, thereby minimizing the risk for injury.

Disadvantages

High Cost, Difficulty, and Inconvenience. Intravenous administration is expensive, difficult, and inconvenient. The cost of IV administration sets and their setup charges can be substantial. Also, setting up an IV line takes time and special training. Because of the difficulty involved, most patients are unable to self-administer IV drugs and therefore must depend

TABLE 4.1 ■ Properties of Major Routes of Drug Administration

Route	Barriers to Absorption	Absorption Pattern	Advantages	Disadvantages
PARENTERAL				
Intravenous (IV)	None (absorption is bypassed)	Instantaneous	Rapid onset, and thus ideal for emergencies Precise control over drug levels Permits use of large fluid volumes Permits use of irritant drugs	Irreversible Expensive Inconvenient Difficult to do, and thus poorly suited for self-administration Risk for fluid overload, infection, and embolism Drug must be water soluble
Intramuscular (IM)	Capillary wall (easy to pass)	Rapid with water-soluble drugs Slow with poorly soluble drugs	Permits use of poorly soluble drugs Permits use of depot preparations	Possible discomfort Inconvenient Potential for injury
Subcutaneous (subQ)	Same as IM	Same as IM	Same as IM	Same as IM
ENTERAL				
Oral (PO)	Epithelial lining of gastrointestinal tract; capillary wall	Slow and variable	Easy Convenient Inexpensive Ideal for self-medication Potentially reversible, and thus safer than parenteral routes	Variability Inactivation of some drugs by gastric acid and digestive enzymes Possible nausea and vomiting from local irritation Patient must be conscious and cooperative

on a healthcare professional. In contrast, oral administration is easy, convenient, and cheap.

Irreversibility. More important than cost or convenience, IV administration can be *dangerous.* Once a drug has been injected, there is no turning back. The drug is in the body and cannot be retrieved. Hence, if the dose is excessive, avoiding harm may be challenging or impossible.

To minimize risk, *most* IV drugs should be injected slowly (over 1 minute or more). Because all of the blood in the body is circulated about once every minute, by injecting a drug over a 1-minute interval, the drug is diluted in the largest volume of blood possible.

Performing IV injections slowly has the additional advantage of reducing the risk for toxicity to the CNS. When a drug is injected into the antecubital vein of the arm, it takes about 15 seconds to reach the brain. Consequently, if the dose is sufficient to cause CNS toxicity, signs of toxicity may become apparent 15 seconds after starting the injection. If the injection is being done slowly (e.g., over a 1-minute interval), only 25% of the total dose will have been administered when signs of toxicity appear. If administration is discontinued immediately, the adverse effects will be much less than they would have been had the entire dose been given.

Fluid Overload. When drugs are administered in a large volume, fluid overload can occur. This can be a significant problem for patients with hypertension, kidney disease, or heart failure.

Infection. Infection can occur from injecting a contaminated drug or from improper technique. Fortunately, the risk for infection is much lower today than it was before the development of modern techniques for sterilizing drugs intended for IV use and the institution of strict standards for the administration of drugs that are given intravenously.

Embolism. Intravenous administration carries a risk for embolism (blood vessel blockage at a site distant from the point of administration). Embolism can be caused in several ways. First, insertion of an IV needle can injure the venous wall, leading to formation of a thrombus (clot); an embolism can result if the clot breaks loose and becomes lodged in another vessel. Second, injection of hypotonic or hypertonic fluids can destroy red blood cells; the debris from these cells can produce embolism.

Finally, injection of drugs that are not fully dissolved can cause embolism. Particles of undissolved drug are like small grains of sand, which can become embedded in blood vessels and cause blockage. Because of the risk for embolism, you should check IV solutions before administering them to ensure that the drugs are in solution. If the fluid is cloudy or contains particles, the drug is not dissolved and must not be administered.

The Importance of Reading Labels. Not all formulations of the same drug are appropriate for IV administration. Accordingly, it is essential to read the label before IV administering a drug. Two examples illustrate why this is so important. The first is insulin. Several types of insulin are now available (e.g., insulin aspart, regular insulin, neutral protamine Hagedorn [NPH] insulin, insulin detemir). Some of these formulations can be IV administered others cannot. Aspart and regular insulin, for example, are safe for IV use. In contrast, NPH and detemir insulin are safe for subQ use, but they could be fatal if IV administered. By checking the label, inadvertent IV injection of particulate insulin can be avoided.

Epinephrine provides our second example of why you should read the label before IV administering a drug. Epinephrine, which stimulates the cardiovascular system, can be injected by several routes (IM, IV, subQ, intracardiac, intraspinal). Be aware, however, that a solution prepared for

use by one route will differ in concentration from a solution prepared for use by other routes. For example, whereas solutions intended for *subQ* administration are *concentrated*, solutions intended for *IV* use are *dilute*. If a solution prepared for subQ use were to be inadvertently administered IV, the result could prove *fatal*. (Intravenous administration of concentrated epinephrine could overstimulate the heart and blood vessels, causing severe hypertension, cerebral hemorrhage, stroke, and death.) The take-home message is that simply giving the *right drug* is not sufficient; you must also be sure that the formulation and concentration are *appropriate for the intended route*.

Intramuscular

Barriers to Absorption. When a drug is IM administered the only barrier to absorption is the *capillary wall*. In capillary beds that serve muscles and most other tissues, there are relatively large spaces between the cells that compose the capillary wall. Drugs can pass through these spaces with ease and need not cross cell membranes to enter the bloodstream. Accordingly, like IV administration, IM administration presents no significant barrier to absorption.

Absorption Pattern. Drugs administered IM may be absorbed rapidly or slowly. The rate of absorption is determined largely by two factors: (1) the water solubility of the drug and (2) blood flow to the site of injection. Drugs that are highly soluble in water will be absorbed rapidly (within 10 to 30 minutes), whereas drugs that are poorly soluble will be absorbed slowly. Similarly, absorption will be rapid from sites where blood flow is high and slow where blood flow is low.

Advantages. The IM route can be used for parenteral administration of *poorly soluble drugs*. Recall that drugs must be dissolved if they are to be administered IV. Consequently, the IV route cannot be used for poorly soluble compounds. In contrast, because little harm will come from depositing a suspension of undissolved drug in the interstitial space of muscle tissue, the IM route is acceptable for drugs whose water solubility is poor.

A second advantage of the IM route is that we can use it to administer *depot preparations* (preparations from which the drug is absorbed slowly over an extended time). Depending on the depot formulation, the effects of a single injection may persist for days, weeks, or even months. For example, *benzathine penicillin G*, a depot preparation of penicillin, can release therapeutically effective amounts of penicillin for a month after a single IM injection. In contrast, a single IM injection of penicillin G itself would be absorbed and excreted in less than 1 day. The obvious advantage of depot preparations is that they can greatly reduce the number of injections required during long-term therapy.

Disadvantages. The major drawbacks of IM administration are discomfort and inconvenience. Intramuscular injection of some preparations can be painful. Also, IM injections can cause local tissue injury and possibly nerve damage (if the injection is done improperly). Lastly, because of bleeding risk, IM injections cannot be used for patients receiving anticoagulant therapy. Like all other forms of parenteral administration, IM injections are less convenient than oral administration.

Subcutaneous. The pharmacokinetics of subQ administration are nearly identical to those of IM administration. As with IM administration, there are no significant barriers to absorption: Once a drug has been injected subQ, it readily enters the blood by passing through the spaces between cells of the capillary wall. As with IM administration, blood flow and drug solubility are the major determinants of how fast absorption takes place. Because of the similarities between subQ and IM administration, these routes have similar advantages (suitability for poorly soluble drugs and depot preparations) and similar drawbacks (discomfort, inconvenience, and potential for injury).

Oral

The abbreviation PO is used in reference to oral administration. This abbreviation stands for *per os*, a Latin phrase meaning *by way of the mouth*.

Barriers to Absorption. After oral administration, drugs may be absorbed from the stomach, the intestine, or both. In either case, there are two barriers to cross: (1) the layer of *epithelial cells* that lines the GI tract, and (2) the *capillary wall*. Because the walls of the capillaries that serve the GI tract offer no significant resistance to absorption, the major barrier to absorption is the GI epithelium. To cross this layer of tightly packed cells, drugs must pass *through* cells rather than between them. For some drugs, intestinal absorption may be *reduced* by *PGP*, a transporter that can pump certain drugs *out* of epithelial cells back into the intestinal lumen.

Absorption Pattern. Because of multiple factors, the rate and extent of drug absorption after oral administration can be *highly variable*. Factors that can influence absorption include (1) the solubility and stability of the drug, (2) gastric and intestinal pH, (3) gastric emptying time, (4) food in the gut, (5) the coadministration of other drugs, and (6) special coatings on the drug preparation.

Drug Movement After Absorption. Before proceeding, we need to quickly review what happens to drugs after their absorption from the GI tract. As depicted in Fig. 4.6,

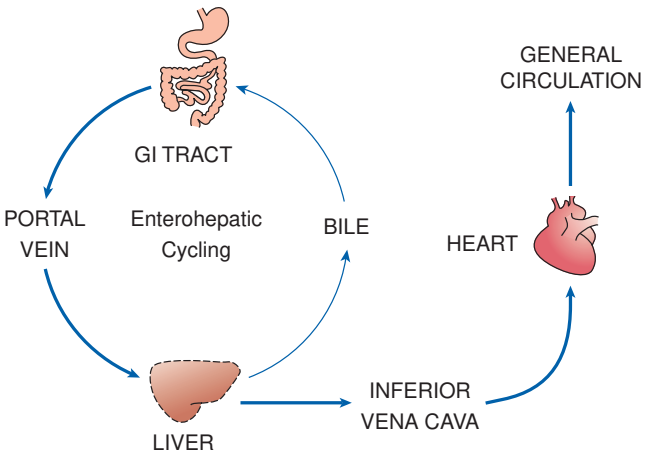

Fig. 4.6 Movement of drugs after gastrointestinal *(GI)* absorption.
All drugs absorbed from sites along the GI tract—stomach, small intestine, and large intestine (but not the oral mucosa or distal rectum)—must go through the liver, via the portal vein, on their way to the heart, and then the general circulation. For some drugs, passage is uneventful. Others undergo extensive hepatic metabolism. Still others undergo *enterohepatic recirculation*, a repeating cycle in which a drug moves from the liver into the duodenum (via the bile duct), and then back to the liver (via the portal blood). As discussed in the text under *Enterohepatic Recirculation*, the process is limited to drugs that have first undergone hepatic glucuronidation.

drugs absorbed from all sites along the GI tract (except the oral mucosa and the distal segment of the rectum) must pass through the liver (via the portal blood) before they can reach the general circulation. For many drugs, this passage is uneventful: They go through the liver, enter the inferior vena cava, and eventually reach the general circulation. Other drugs undergo extensive hepatic metabolism. Still others may undergo *enterohepatic recirculation*, a repeating cycle in which a drug moves from the liver into the duodenum (via the bile duct), and then back to the liver (via the portal blood). This cycle is discussed further under *Enterohepatic Recirculation*.

Advantages. Oral administration is easy and convenient. This makes it the preferred route for self-medication.

Although absorption of oral drugs can be highly variable, this route is still *safer than injection*. With oral administration, there is no risk for fluid overload, infection, or embolism. Furthermore, because oral administration is potentially reversible, whereas injections are not, oral administration is safer. Recall that with parenteral administration there is no turning back. Once a drug has been injected, there is little we can do to prevent absorption and subsequent effects. In contrast, if need be, there are steps we can take to prevent absorption after inappropriate oral administration. For example, we can decrease absorption by giving activated charcoal, a compound that adsorbs (soaks up) drugs while they are still in the GI tract. Once drugs are adsorbed onto the charcoal, they cannot be absorbed into the bloodstream. This ability to prevent the absorption of orally administered drugs gives oral medications a safety factor that is unavailable with drugs given by injection.

Disadvantages

Variability. The major disadvantage of oral therapy is that absorption can be highly variable. That is, a drug administered to patient A may be absorbed rapidly and completely, whereas the same drug given to patient B may be absorbed slowly and incompletely. This variability makes it difficult to control the concentration of a drug at its sites of action and therefore makes it difficult to control the onset, intensity, and duration of responses.

Inactivation. Oral administration can lead to inactivation of certain drugs. Penicillin G, for example, cannot be taken orally because it would be destroyed by stomach acid. Similarly, insulin cannot be taken orally because it would be destroyed by digestive enzymes. Other drugs (e.g., nitroglycerin) undergo extensive inactivation as they pass through the liver, a phenomenon known as the *first-pass effect* (see *Special Considerations in Drug Metabolism*).

Patient Requirements. Oral drug administration requires a conscious, cooperative patient. Drugs cannot be administered orally to comatose individuals or to individuals who, for whatever reason (e.g., psychosis, seizure, obstinacy, nausea), are unable or unwilling to swallow medication.

Local Irritation. Some oral preparations cause local irritation of the GI tract, which can result in discomfort, nausea, and vomiting.

Comparing Oral Administration With Parenteral Administration

Because of ease, convenience, and relative safety, *oral administration is generally preferred to parenteral administration*. Nevertheless, there *are* situations in which parenteral administration may be superior:

- Emergencies that require rapid onset of drug action.
- Situations in which plasma drug levels must be tightly controlled. (Because of variable absorption, oral administration does not permit tight control of drug levels.)
- Treatment with drugs that would be destroyed by gastric acidity, digestive enzymes, or hepatic enzymes if given orally (e.g., insulin, penicillin G, nitroglycerin).
- Treatment with drugs that would cause severe local injury if administered by mouth (e.g., certain anticancer agents).
- Treating a systemic disorder with drugs that cannot cross membranes (e.g., quaternary ammonium compounds).
- Treating conditions for which the prolonged effects of a depot preparation might be desirable.
- Treating patients who cannot or will not take drugs orally.

Pharmaceutical Preparations for Oral Administration

There are several kinds of "packages" (formulations) into which a drug can be put for oral administration. Three such formulations—*tablets, enteric-coated preparations*, and *sustained-release preparations*—are discussed in the sections that follow.

Before we discuss drug formulations, it will be helpful to define two terms: *chemical equivalence* and *bioavailability*. Drug preparations are considered *chemically equivalent* if they contain the same amount of the identical chemical compound (drug). Preparations are considered equal in *bioavailability* if the drug they contain is absorbed at the same rate and to the same extent. Please note that it is possible for two formulations of the same drug to be chemically equivalent but differing in bioavailability.

Tablets

A tablet is a mixture of a drug plus binders and fillers, all of which have been compressed together. Tablets made by different manufacturers may differ in their rates of disintegration and dissolution, causing differences in bioavailability. As a result, two tablets that contain the same amount of the same drug may differ with respect to onset and intensity of effects.

Enteric-Coated Preparations

Enteric-coated preparations consist of drugs that have been covered with a material designed to dissolve in the intestine but not the stomach. Materials used for enteric coatings include fatty acids, waxes, and shellac. Because enteric-coated preparations release their contents into the intestine and not the stomach, these preparations are employed for two general purposes: (1) to protect drugs from acid and pepsin in the stomach and (2) to protect the stomach from drugs that can cause gastric discomfort.

The primary disadvantage of enteric-coated preparations is that absorption can be even more variable than with standard tablets. Because gastric emptying time can vary from minutes up to 12 hours and because enteric-coated preparations cannot be absorbed until they leave the stomach, variations in gastric emptying time can alter time of onset. Furthermore, enteric coatings sometimes fail to dissolve, thereby allowing medication to pass through the GI tract without being absorbed at all.

Sustained-Release Preparations

Sustained-release formulations are capsules filled with tiny spheres that contain the actual drug; the individual spheres

have coatings that dissolve at variable rates. Because some spheres dissolve more slowly than others, the drug is released steadily throughout the day. The primary advantage of sustained-release preparations is that they permit a reduction in the number of daily doses. These formulations have the additional advantage of producing relatively steady drug levels over an extended time (much like giving a drug by infusion). The major disadvantages of sustained-release formulations are the high cost and potential for variable absorption.

Blood Flow to Tissues

In the first phase of distribution, drugs are carried by the blood to the tissues and organs of the body. The rate at which drugs are delivered to a particular tissue is determined by blood flow to that tissue. Because most tissues are well perfused, regional blood flow is rarely a limiting factor in drug distribution.

There are two pathologic conditions—abscesses and tumors—in which low regional blood flow can affect drug therapy. An abscess is a pus-filled pocket of infection that has no internal blood vessels. Because abscesses lack a blood supply, antibiotics cannot reach the bacteria within. Accordingly, if drug therapy is to be effective, the abscess must first be surgically drained.

Solid tumors have a limited blood supply. Although blood flow to the outer regions of tumors is relatively high, blood flow becomes progressively lower toward the core. As a result, it may not be possible to achieve high drug levels deep inside tumors. Limited blood flow is a major reason why solid tumors are resistant to drug therapy.

Additional Routes of Administration

Drugs can be administered by a number of routes in addition to those already discussed. Drugs can be applied *topically* for local therapy of the skin, eyes, ears, nose, mouth, rectum, and vagina. In a few cases, topical agents (e.g., nitroglycerin, nicotine, testosterone, estrogen) are formulated for *transdermal* absorption into the systemic circulation. Some drugs are *inhaled* to elicit local effects in the lungs, especially in the treatment of asthma. Other inhalational agents (e.g., volatile anesthetics, oxygen) are used for their systemic effects. *Rectal suppositories* may be employed for local effects or for effects throughout the body. *Vaginal suppositories* may be employed to treat local disorders. For management of some conditions, drugs must be given by *direct injection into a specific site* (e.g., heart, joints, nerves, CNS). The unique characteristics of these routes are addressed throughout the book as we discuss the specific drugs that employ them.

DISTRIBUTION

Distribution is defined as drug movement from the blood to the interstitial space of tissues, and from there into cells. Drug distribution is determined by three major factors: blood flow to tissues; the ability of a drug to exit the vascular system; and, to a lesser extent, the ability of a drug to enter cells.

Exiting the Vascular System

After a drug has been delivered to an organ or tissue via the blood, the next step is to exit the vasculature. Because most drugs do not produce their effects within the blood, the ability to leave the vascular system is an important determinant of drug actions. Exiting the vascular system is also necessary for drugs to undergo metabolism and excretion. Drugs in the vascular system leave the blood at capillary beds.

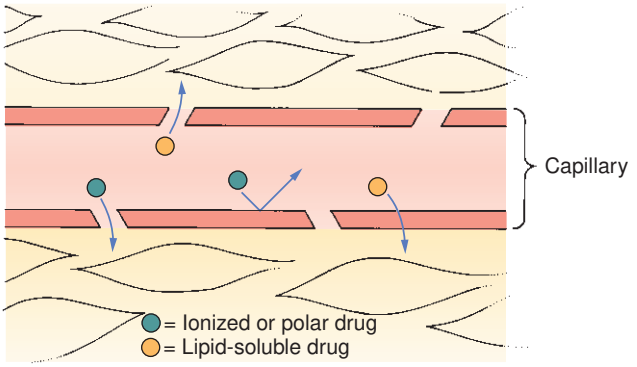

Fig. 4.7 Drug movement at typical capillary beds. In most capillary beds, "large" gaps exist between the cells that compose the capillary wall. Drugs and other molecules can pass freely into and out of the bloodstream through these gaps. As illustrated, lipid-soluble compounds can also pass directly through the cells of the capillary wall.

Typical Capillary Beds

Most capillary beds offer no resistance to the departure of drugs. Why? Because, in most tissues, drugs can leave the vasculature simply by passing through pores in the capillary wall. Because drugs pass *between* capillary cells rather than *through* them, movement into the interstitial space is not impeded. The exit of drugs from a typical capillary bed is depicted in Fig. 4.7.

The Blood-Brain Barrier

The term *blood-brain barrier* (BBB) refers to the unique anatomy of capillaries in the CNS. As shown in Fig. 4.8, there are *tight junctions* between the cells that compose the walls of most capillaries in the CNS. These junctions are so tight that they prevent drug passage. Consequently, to leave the blood and reach sites of action within the brain, a drug must be able to pass *through* cells of the capillary wall. Only drugs that are *lipid soluble* or have a *transport system* can cross the BBB to a significant degree.

Recent evidence indicates that, in addition to tight junctions, the BBB has another protective component: *PGP*. As noted earlier, PGP is a transporter that pumps a variety of drugs out of cells. In capillaries of the CNS, PGP pumps drugs back into the blood and thereby limits their access to the brain.

The presence of the BBB is a mixed blessing. The good news is that the barrier protects the brain from injury by potentially toxic substances. The bad news is that the barrier can be a significant obstacle to therapy of CNS disorders. The barrier can, for example, impede access of antibiotics to CNS infections.

The BBB is not fully developed at birth. As a result, newborns have heightened sensitivity to medicines that act on the brain. Likewise, neonates are especially vulnerable to CNS toxicity.

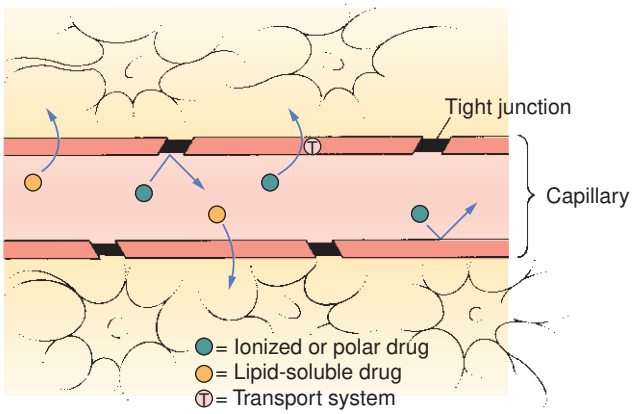

Fig. 4.8 ▪ Drug movement across the blood-brain barrier. Tight junctions between cells that compose the walls of capillaries in the central nervous system (CNS) prevent drugs from passing between cells to exit the vascular system. Consequently, to reach sites of action within the brain, a drug must pass directly through cells of the capillary wall. To do this, the drug must be lipid soluble or able to use an existing transport system.

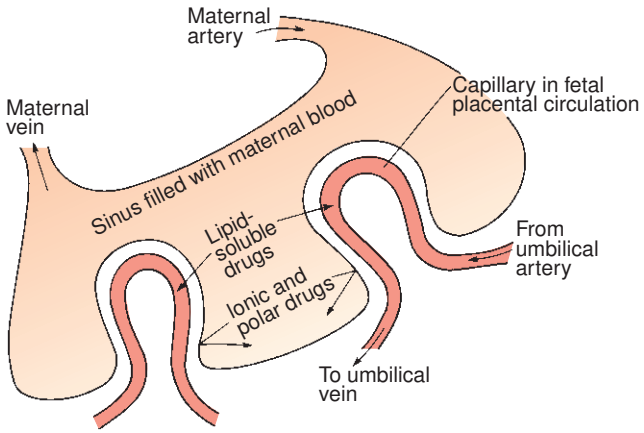

Fig. 4.9 ▪ Placental drug transfer. To enter the fetal circulation, drugs must cross membranes of the maternal and fetal vascular systems. Lipid-soluble drugs can readily cross these membranes and enter the fetal blood, whereas ions and polar molecules are prevented from reaching the fetal blood.

Placental Drug Transfer

The membranes of the placenta separate the maternal circulation from the fetal circulation (Fig. 4.9). *Nevertheless, the membranes of the placenta do NOT constitute an absolute barrier to the passage of drugs*. The same factors that determine the movement of drugs across other membranes determine the movement of drugs across the placenta. Accordingly, lipid-soluble, nonionized compounds readily pass from the maternal bloodstream into the blood of the fetus. In contrast, compounds that are ionized, highly polar, or protein bound (see the following discussion) are largely excluded—as are drugs that are substrates for PGP, a transporter that can pump a variety of drugs out of placental cells into the maternal blood.

Drugs that have the ability to cross the placenta can cause serious harm. Some compounds can cause birth defects, ranging from low birth weight to physical anomalies and alterations in mental aptitude. If a pregnant woman is a habitual user of opioids (e.g., heroin), her child will be born drug dependent and will need treatment to prevent withdrawal. The use of respiratory depressants (anesthetics and analgesics) during delivery can depress respiration in the neonate. Accordingly, infants exposed to respiratory depressants must be monitored very closely until breathing has normalized.

Protein Binding

Drugs can form reversible bonds with various proteins in the body. Of all the proteins with which drugs can bind, *plasma albumin* is the most important, being the most abundant protein in plasma. Like other proteins, albumin is a large molecule, having a molecular weight of 69,000 daltons. Because of its size, *albumin always remains in the bloodstream*. Albumin is too large to squeeze through pores in the capillary wall, and no transport system exists by which it might leave.

Fig. 4.10A depicts the binding of drug molecules to albumin. Note that the drug molecules are much smaller than albumin. (The molecular mass of the average drug is about 300 to 500 daltons compared with 69,000 daltons for albumin.) As indicated by the two-way arrows, binding between albumin and drugs is *reversible*. Hence, drugs may be *bound* or *unbound* (free).

Even though a drug can bind albumin, only some molecules will be bound at any moment. The percentage of drug molecules that are bound is determined by the strength of the attraction between albumin and the drug. For example, the attraction between albumin and warfarin (an anticoagulant) is strong, causing nearly all (99%) of the warfarin molecules in plasma to be bound, leaving only 1% free. For gentamicin (an antibiotic), the ratio of bound to free is quite different; because the attraction between gentamicin and albumin is relatively weak, less than 10% of the gentamicin molecules in plasma are bound, leaving more than 90% free.

An important consequence of protein binding is restriction of drug distribution. Because albumin is too large to leave the bloodstream, drug molecules that are bound to albumin cannot leave either (see Fig. 4.10B). As a result, bound molecules cannot reach their sites of action or undergo metabolism or excretion until the drug-protein bond is broken. This prolongs the distribution phase and increases the drug's half-life. (The concept of drug half-life is discussed later in this chapter.)

In addition to restricting drug distribution, protein binding can be a source of drug interactions. As suggested by Fig. 4.10A, each molecule of albumin has only a few sites to which drug molecules can bind. Because the number of binding sites is limited, drugs with the ability to bind albumin will compete with one another for those sites. As a result, one drug can displace another from albumin, causing the free concentration of the displaced drug to rise. By increasing levels of free drug, competition for binding can increase the intensity of drug responses. If plasma drug levels rise sufficiently, toxicity can result.

Entering Cells

Some drugs must enter cells to reach their sites of action, and practically all drugs must enter cells to undergo metabolism and excretion. The factors that determine the ability of a drug

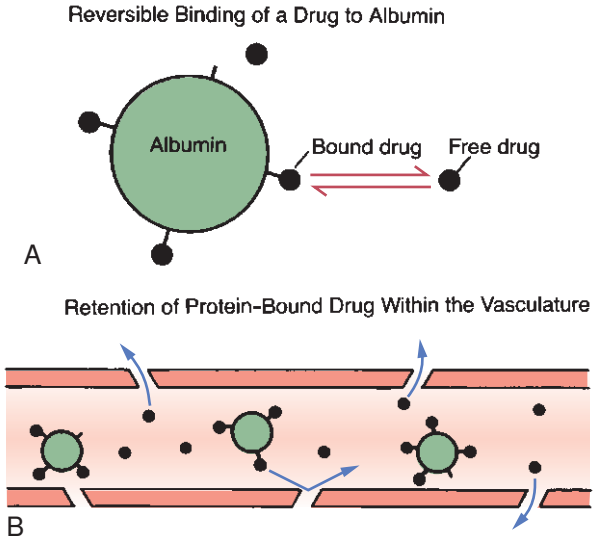

Fig. 4.10 ■ Protein binding of drugs.
A, Albumin is the most prevalent protein in plasma and the most important of the proteins to which drugs bind. **B,** Only unbound (free) drug molecules can leave the vascular system. Bound molecules are too large to fit through the pores in the capillary wall.

to cross cell membranes are the same factors that determine the passage of drugs across all other membranes, namely, lipid solubility, the presence of a transport system, or both.

As discussed in Chapter 5, many drugs produce their effects by binding with receptors located on the external surface of the cell membrane. Obviously, these drugs do not need to cross the cell membrane to act.

METABOLISM

Drug metabolism, also known as *biotransformation*, is defined as *the chemical alteration of drug structure*. Most drug metabolism takes place in the liver.

Hepatic Drug-Metabolizing Enzymes

Most drug metabolism that takes place in the liver is performed by the *hepatic microsomal enzyme system*, also known as the *P450 system*. The term *P450* refers to *cytochrome P450*, a key component of this enzyme system.

It is important to appreciate that cytochrome P450 is not a single molecular entity but rather a group of 12 closely related enzyme families. Three of the cytochrome P450 (CYP) families—designated CYP1, CYP2, and CYP3—metabolize drugs. The other nine families metabolize endogenous compounds (e.g., steroids, fatty acids). Every one of the three P450 families that metabolize drugs is itself composed of multiple forms, each of which metabolizes only certain drugs. To identify the individual forms of cytochrome P450, designations such as CYP1A2, CYP2D6, and CYP3A4 are used to indicate specific members of the CYP1, CYP2, and CYP3 families, respectively.

Hepatic microsomal enzymes are capable of catalyzing a wide variety of reactions. Some of these reactions are illustrated in Fig. 4.11. As these examples indicate, drug metabolism does not always result in the breakdown of drugs into smaller molecules; drug metabolism can also result in the synthesis of a molecule that is larger than the parent drug.

Therapeutic Consequences of Drug Metabolism

Drug metabolism has six possible consequences of therapeutic significance:

- Accelerated renal excretion of drugs
- Drug inactivation
- Increased therapeutic action
- Activation of "prodrugs"
- Increased toxicity
- Decreased toxicity

The reactions shown in Fig. 4.11 illustrate these outcomes.

Accelerated Renal Drug Excretion

The most important consequence of drug metabolism is promotion of renal drug excretion. As discussed under *Renal Drug Excretion* later in this chapter, the kidneys, which are the major organs of drug excretion, are unable to excrete drugs that are highly lipid soluble. Hence, by converting lipid-soluble drugs into more hydrophilic (water-soluble) forms, metabolic conversion can accelerate the renal excretion of many agents. For certain highly lipid-soluble drugs (e.g., thiopental), complete renal excretion would take years were it not for their conversion into more hydrophilic forms.

What kinds of metabolic transformations enhance excretion? Two important mechanisms are shown in Fig. 4.11, panels *1A* and *1B*. In panel *1A*, a simple structural change (addition of a hydroxyl group) converts pentobarbital into a more polar (less lipid-soluble) form. In panel *1B*, a highly lipophilic drug (phenytoin) is converted into a highly hydrophilic form by undergoing *glucuronidation*, a process in which a hydrophilic glucose derivative (glucuronic acid) is attached to phenytoin. As a result of glucuronidation, phenytoin is rendered much more water soluble and hence can be rapidly excreted by the kidneys.

It should be noted that not all glucuronides are excreted by the kidneys. In many cases, glucuronidated drugs are secreted into the bile and then transported to the duodenum (via the bile duct), after which they can undergo excretion in the feces. Nevertheless, in some cases, secretion into the bile can result in *enterohepatic recirculation* (discussed later in this chapter).

Drug Inactivation

Drug metabolism can convert pharmacologically active compounds into inactive forms. This process is illustrated by the conversion of procaine (a local anesthetic) into *para*-aminobenzoic acid (PABA), an inactive metabolite (see Fig. 4.11, panel *2*).

Increased Therapeutic Action

Metabolism can increase the effectiveness of some drugs. This concept is illustrated by the conversion of codeine into morphine (see Fig. 4.11, panel *3*). The analgesic activity of

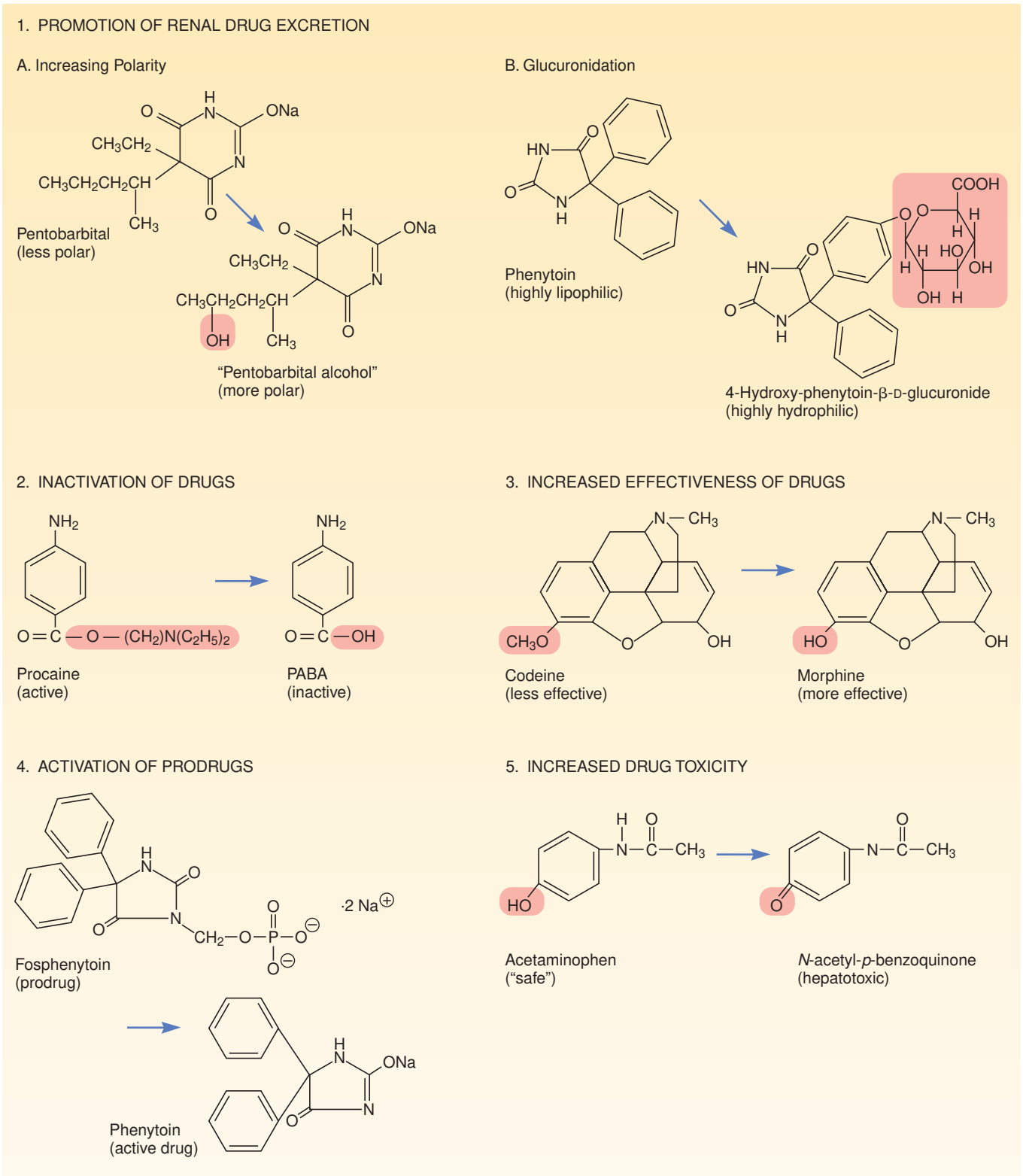

Fig. 4.11 ▪ **Therapeutic consequences of drug metabolism.**
***PABA, para*-aminobenzoic acid.**

morphine is so much greater than that of codeine that formation of morphine may account for virtually all the pain relief that occurs after codeine administration.

Activation of Prodrugs

A *prodrug* is a compound that is pharmacologically inactive as administered, and then undergoes conversion into its active form via metabolism. Activation of a prodrug is illustrated by the metabolic conversion of fosphenytoin into phenytoin (see Fig. 4.11, panel *4*).

Increased or Decreased Toxicity

By converting drugs into inactive forms, metabolism can decrease toxicity. Conversely, metabolism can increase the potential for harm by converting relatively safe compounds into forms that are toxic. Increased toxicity is illustrated by the conversion of acetaminophen [Tylenol, others] into a hepatotoxic metabolite (see Fig. 4.11, panel *5*). It is this product of metabolism, and not acetaminophen itself, that causes injury when acetaminophen is taken in overdose.

Special Considerations in Drug Metabolism

Several factors can influence the rate at which drugs are metabolized. These must be accounted for in drug therapy.

Age

The drug-metabolizing capacity of infants is limited. The liver does not develop its full capacity to metabolize drugs until about 1 year after birth. During the time before hepatic maturation, infants are especially sensitive to drugs, and care must be taken to avoid injury. Similarly, the ability of older adults to metabolize drugs is commonly decreased. Drug dosages may need to be reduced to prevent drug toxicity.

Induction and Inhibition of Drug-Metabolizing Enzymes

Drugs may be P450 substrates, P450 enzyme inducers, or P450 enzyme inhibitors. Often, a drug may have more than one property. For example, a drug may be both a substrate and an inducer.

Drugs that are metabolized by P450 hepatic enzymes are substrates. The rate at which substrates are metabolized is affected by drugs that act as P450 inducers or inhibitors.

Inducers are drugs that act on the liver to increase rates of drug metabolism. This process of stimulating enzyme synthesis is known as *induction*. As the rate of drug metabolism increases, plasma drug levels fall.

Induction of drug-metabolizing enzymes can have two therapeutic consequences. First, if the inducer is also a substrate, by stimulating the liver to produce more drug-metabolizing enzymes, the drug can increase the rate of its own metabolism, thereby necessitating an increase in its dosage to maintain therapeutic effects. Second, induction of drug-metabolizing enzymes can accelerate the metabolism of other substrates used concurrently, necessitating an increase in their dosages.

Inhibitors are drugs that act on the liver to decrease rates of drug metabolism. This process is known as *inhibition*. These drugs also create therapeutic consequences because slower metabolism can cause an increase in active drug accumulation. This can lead to an increase in adverse effects and toxicity.

First-Pass Effect

The term *first-pass effect* refers to the rapid hepatic inactivation of certain oral drugs. When drugs are absorbed from the GI tract, they are carried directly to the liver via the hepatic portal vein. If the capacity of the liver to metabolize a drug is extremely high, that drug can be completely inactivated on its first pass through the liver. As a result, no therapeutic effects can occur. To circumvent the first-pass effect, a drug that undergoes rapid hepatic metabolism is often administered parenterally. This permits the drug to temporarily bypass the liver, thereby allowing it to reach therapeutic levels in the systemic circulation.

Nitroglycerin is the classic example of a drug that undergoes such rapid hepatic metabolism that it is largely without effect after oral administration. When administered sublingually (under the tongue), however, nitroglycerin is very active. Sublingual administration is effective because it permits nitroglycerin to be absorbed directly into the systemic circulation. Once in the circulation, the drug is carried to its sites of action before passage through the liver. Hence, therapeutic action can be exerted before the drug is exposed to hepatic enzymes.

Nutritional Status

Hepatic drug-metabolizing enzymes require a number of cofactors to function. In the malnourished patient, these cofactors may be deficient, causing drug metabolism to be compromised.

Competition Between Drugs

When two drugs are metabolized by the same metabolic pathway, they may compete with each other for metabolism and may, thereby, decrease the rate at which one or both agents are metabolized. If metabolism is depressed enough, a drug can accumulate to dangerous levels.

Enterohepatic Recirculation

As noted earlier and depicted in Fig. 4.7, enterohepatic recirculation is a repeating cycle in which a drug is transported from the liver into the duodenum (via the bile duct), and then back to the liver (via the portal blood). It is important to note, however, that only certain drugs are affected. Specifically, the process is limited to drugs that have undergone *glucuronidation* (see Fig. 4.11, panel *1B*). After glucuronidation, these drugs can enter the bile, and then pass to the duodenum. Once there, they can be hydrolyzed by intestinal beta-glucuronidase, an enzyme that breaks the bond between the original drug and the glucuronide moiety, thereby releasing the free drug. Because the free drug is more lipid soluble than the glucuronidated form, the free drug can undergo reabsorption across the intestinal wall, followed by transport back to the liver, where the cycle can start again. Because of enterohepatic recycling, drugs can remain in the body much longer than they otherwise would.

Some glucuronidated drugs do not undergo extensive recycling. Glucuronidated drugs that are more stable to hydrolysis will be excreted intact in the feces, without significant recirculation.

EXCRETION

Drug excretion is defined as *the removal of drugs from the body*. Drugs and their metabolites can exit the body in urine, bile, sweat, saliva, breast milk, and expired air. The most important organ for drug excretion is the kidney.

Renal Drug Excretion

The kidneys account for the excretion of most drugs. When the kidneys are healthy, they serve to limit the duration of action of many drugs. Conversely, if renal failure occurs, both the duration and intensity of drug responses may increase.

Steps in Renal Drug Excretion

Urinary excretion is the net result of three processes: (1) glomerular filtration, (2) passive tubular reabsorption, and (3) active tubular secretion (Fig. 4.12).

Glomerular Filtration. Renal excretion begins at the glomerulus of the kidney tubule. The glomerulus consists of a capillary network surrounded by Bowman's capsule; small pores perforate the capillary walls. As blood flows through the glomerular capillaries, fluids and small molecules—including drugs—are forced through the pores of the capillary wall. This process, called glomerular filtration, moves drugs from the blood into the tubular urine. Blood cells and large molecules (e.g., proteins) are too big to pass through the capillary pores and therefore do not undergo filtration. Because large molecules are not filtered, drugs bound to albumin remain behind in the blood.

Passive Tubular Reabsorption. As depicted in Fig. 4.12, the vessels that deliver blood to the glomerulus return to proximity with the renal tubule at a point distal to the glomerulus. At this distal site, drug concentrations in the blood are lower than drug concentrations in the tubule. This concentration gradient acts as a driving force to move drugs from the lumen of the tubule back into the blood. Because lipid-soluble drugs can readily cross the membranes that compose the tubular and vascular walls, *drugs that are lipid soluble undergo passive reabsorption from the tubule back into the blood.* In contrast, drugs that are not lipid soluble (ions and polar compounds) remain in the urine to be excreted. By converting lipid-soluble drugs into more polar forms, drug metabolism reduces passive reabsorption of drugs and thereby accelerates their excretion.

Active Tubular Secretion. There are active transport systems in the kidney tubules that pump drugs from the blood to the tubular urine. The tubules have two primary classes of pumps, one for organic acids and one for organic bases. In addition, tubule cells contain PGP, which can pump a variety of drugs into the urine. These pumps have a relatively high capacity and play a significant role in excreting certain compounds.

Factors That Modify Renal Drug Excretion

pH-Dependent Ionization. The phenomenon of pH-dependent ionization can be used to accelerate the renal excretion of drugs. Recall that passive tubular reabsorption is limited to lipid-soluble compounds. Because ions are not lipid soluble, drugs that are ionized at the pH of tubular urine will remain in the tubule and be excreted. Consequently, by manipulating urinary pH in such a way as to promote the ionization of a drug, we can decrease passive reabsorption back into the blood and can thereby hasten the drug's elimination. This principle has been employed to promote the excretion of poisons as well as medications that have been taken in toxic doses.

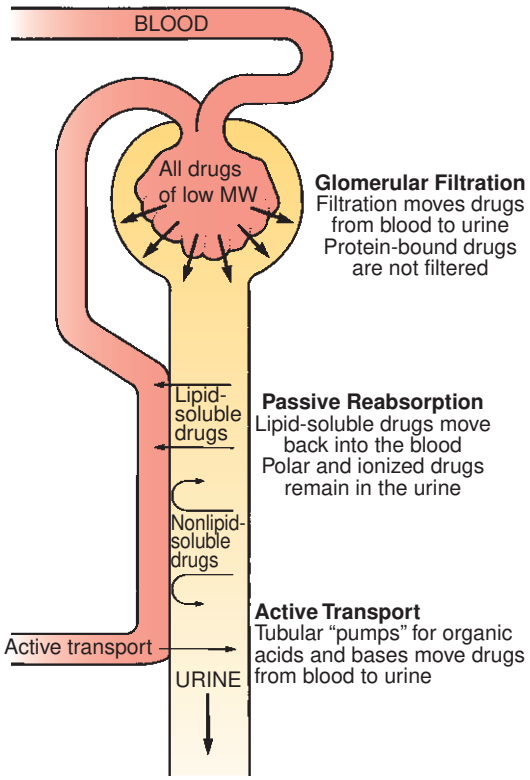

Fig. 4.12 ■ Renal drug excretion.
MW, Molecular weight.

The treatment of aspirin poisoning provides an example of how manipulation of urinary pH can be put to therapeutic advantage. When children have been exposed to toxic doses of aspirin, they can be treated, in part, by giving them an agent that elevates urinary pH (i.e., makes the urine more basic). Because aspirin is an acidic drug and because acids tend to ionize in basic media, elevation of urinary pH causes more of the aspirin molecules in urine to become ionized. As a result, less drug is passively reabsorbed; therefore more is excreted.

Competition for Active Tubular Transport. Competition between drugs for active tubular transport can delay renal excretion, thereby prolonging effects. The active transport systems of the renal tubules can be envisioned as motor-driven revolving doors that carry drugs from the plasma into the renal tubules. These "revolving doors" can carry only a limited number of drug molecules per unit of time. Accordingly, if there are too many molecules present, some must wait their turn. Because of competition, if we administer two drugs at the same time, and if both use the same transport system, excretion of each will be delayed by the presence of the other.

Competition for transport has been employed clinically to prolong the effects of drugs that normally undergo rapid renal excretion. For example, when administered alone, penicillin is rapidly cleared from the blood by active tubular transport. Excretion of penicillin can be delayed by concurrent administration of probenecid, an agent that is removed from the blood by the same tubular transport system that pumps penicillin. Hence, if a large dose of probenecid is administered, renal

excretion of penicillin will be delayed while the transport system is occupied with moving the probenecid. Years ago, when penicillin was expensive to produce, combined use with probenecid was common. Today, penicillin is cheap. As a result, rather than using probenecid to preserve penicillin levels, penicillin is simply given in larger doses.

Age. The kidneys of newborns are not fully developed. Until their kidneys reach full capacity (a few months after birth), infants have a limited capacity to excrete drugs. This must be accounted for when medicating an infant.

In old age, renal function often declines. Older adults have smaller kidneys and fewer nephrons. The loss of nephrons results in decreased blood filtration. Additionally, vessel changes, such as atherosclerosis, reduce renal blood flow. As a result, renal excretion of drugs is decreased.

Nonrenal Routes of Drug Excretion

In most cases, excretion of drugs by nonrenal routes has minimal clinical significance. In certain situations, however, nonrenal excretion can have important therapeutic and toxicologic consequences.

Breast Milk

Drugs taken by breast-feeding women can undergo excretion into milk. As a result, breast-feeding can expose the nursing infant to drugs. The factors that influence the appearance of drugs in breast milk are the same factors that determine the passage of drugs across membranes. Accordingly, lipid-soluble drugs have ready access to breast milk, whereas drugs that are polar, ionized, or protein bound cannot enter in significant amounts. Because infants may be harmed by drugs excreted in breast milk, nursing mothers should avoid all unnecessary drugs. If a woman *must* take medication, she should consult with her prescriber to ensure that the drug will not reach concentrations in her milk high enough to harm her baby.

Other Nonrenal Routes of Excretion

The *bile* is an important route of excretion for certain drugs. Recall that bile is secreted into the small intestine, and then leaves the body in the feces. In some cases, drugs entering the intestine in bile may undergo reabsorption back into the portal blood. This reabsorption, referred to as *enterohepatic recirculation*, can substantially prolong a drug's sojourn in the body (see *Enterohepatic Recirculation*, discussed previously).

The *lungs* are the major route by which volatile anesthetics are excreted.

Small amounts of drugs can appear in *sweat* and *saliva*. These routes have little therapeutic or toxicologic significance.

TIME COURSE OF DRUG RESPONSES

It is possible to regulate the time at which drug responses start, the time they are most intense, and the time they cease. Because the four pharmacokinetic processes—absorption, distribution, metabolism, and excretion—determine how much drug will be at its sites of action at any given time, these processes are the major determinants of the time course over which drug responses take place.

Plasma Drug Levels

In most cases, the time course of drug action bears a direct relationship to the concentration of a drug in the blood. Hence, before discussing the time course per se, we need to review several important concepts related to plasma drug levels.

Clinical Significance of Plasma Drug Levels

Clinicians frequently monitor plasma drug levels in an effort to regulate drug responses. When measurements indicate that drug levels are inappropriate, these levels can be adjusted up or down by changing dose size, dose timing, or both.

The practice of regulating plasma drug levels to control drug responses should seem a bit odd, given that (1) drug responses are related to drug concentrations at sites of action, and that (2) the site of action of most drugs is not in the blood. The question arises, "Why adjust plasma levels of a drug when what really matters is the concentration of that drug at its sites of action?" The answer begins with the following observation: More often than not, it is a practical impossibility to measure drug concentrations at sites of action. For example, when a patient with seizures takes phenytoin (an antiseizure agent), we cannot routinely draw samples from inside the brain to see whether levels of the medication are adequate for seizure control. Fortunately, in the case of phenytoin and most other drugs, it is not necessary to measure drug concentrations at actual sites of action to have an objective basis for adjusting dosage. Experience has shown that, for most drugs, *there is a direct correlation between therapeutic and toxic responses and the amount of drug present in plasma*. Therefore, although we can't usually measure drug concentrations at sites of action, we *can* determine plasma drug concentrations that, in turn, are highly predictive of therapeutic and toxic responses. Accordingly, the dosing objective is commonly spoken of in terms of achieving a specific plasma level of a drug.

Two Plasma Drug Levels Defined

Two plasma drug levels are of special importance: (1) the minimum effective concentration and (2) the toxic concentration. These levels are depicted in Fig. 4.13 and defined in the following sections.

Minimum Effective Concentration

The minimum effective concentration (MEC) is defined as *the plasma drug level below which therapeutic effects will not occur*. Hence, to be of benefit, a drug must be present in concentrations at or above the MEC.

Toxic Concentration. Toxicity occurs when plasma drug levels climb too high. The plasma level at which toxic effects begin is termed the *toxic concentration*. Doses must be kept small enough so that the toxic concentration is not reached.

Therapeutic Range

As indicated in Fig. 4.13, there is a range of plasma drug levels, falling between the MEC and the toxic concentration, that is termed the *therapeutic range*. When plasma levels are within the therapeutic range, there is enough drug present to produce therapeutic responses but not so much that toxicity results. *The objective of drug dosing is to maintain plasma drug levels within the therapeutic range*.

The width of the therapeutic range is a major determinant of the ease with which a drug can be used safely.

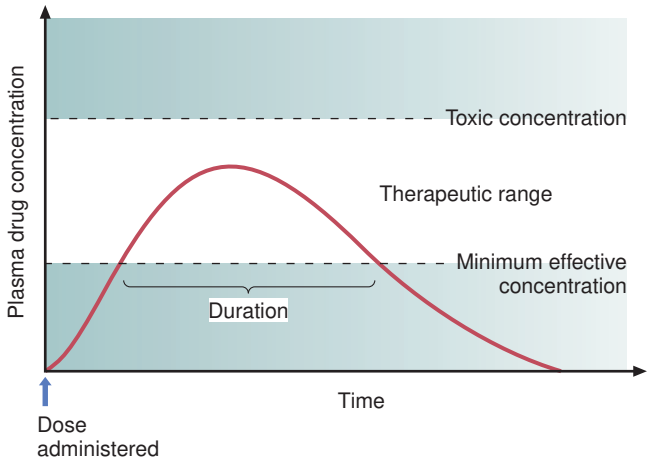

Fig. 4.13 ▪ **Single-dose time course.**

Drugs that have a narrow therapeutic range are difficult to administer safely. Conversely, drugs that have a wide therapeutic range can be administered safely with relative ease. Acetaminophen, for example, has a relatively wide therapeutic range: The toxic concentration is about 30 times greater than the MEC. Because of this wide therapeutic range, the dosage does not need to be highly precise; a broad range of doses can be employed to produce plasma levels that will be above the MEC and below the toxic concentration. In contrast, lithium (used for bipolar disorder) has a very narrow therapeutic range: The toxic concentration is only three times greater than the MEC. Because toxicity can result from lithium levels that are not much greater than those needed for therapeutic effects, lithium dosing must be done carefully. If lithium had a wider therapeutic range, the drug would be much easier to use.

Understanding the concept of therapeutic range can facilitate patient care. Because drugs with a narrow therapeutic range are more dangerous than drugs with a wide therapeutic range, patients taking drugs with a narrow therapeutic range are the most likely to require intervention for drug-related complications. The nurse who is aware of this fact can focus additional attention on monitoring these patients for signs and symptoms of toxicity.

Single-Dose Time Course

Fig. 4.13 shows how plasma drug levels change over time after a single dose of an oral medication. Drug levels rise as the medicine undergoes absorption. Drug levels then decline as metabolism and excretion eliminate the drug from the body.

Because responses cannot occur until plasma drug levels have reached the MEC, there is a latent period between drug administration and the onset of effects. The extent of this delay is determined by the rate of absorption.

The duration of effects is determined largely by the combination of metabolism and excretion. As long as drug levels remain above the MEC, therapeutic responses will be maintained; when levels fall below the MEC, benefits will cease. Because metabolism and excretion are the processes most responsible for causing plasma drug levels to fall, these processes are the primary determinants of how long drug effects will persist.

Drug Half-Life

Before proceeding to the topic of multiple dosing, we need to discuss the concept of a half-life. When a patient ceases drug use, the combination of metabolism and excretion will cause the amount of drug in the body to decline. The half-life of a drug is an index of just how rapidly that decline occurs.

Drug half-life is defined as *the time required for the amount of drug in the body to decrease by 50%*. A few drugs have half-lives that are extremely short—on the order of minutes. In contrast, the half-lives of some drugs exceed 1 week. Drugs with short half-lives leave the body quickly. Drugs with long half-lives leave slowly.

Note that, in our definition of half-life, a *percentage*—not a specific *amount*—of drug is lost during one half-life. That is, the half-life does not specify, for example, that 2 gm or 18 mg will leave the body in a given time. Rather, the half-life tells us that, no matter what the amount of drug in the body may be, half (50%) will leave during a specified period of time (the half-life). The actual amount of drug that is lost during one half-life depends on just how much drug is present: The more drug that is in the body, the larger the amount lost during one half-life.

The concept of half-life is best understood through an example. Morphine provides a good illustration. The half-life of morphine is approximately 3 hours. By definition, this means that body stores of morphine will decrease by 50% every 3 hours, regardless of how much morphine is in the body. If there are 50 mg of morphine in the body, 25 mg (50% of 50 mg) will be lost in 3 hours; if there are only 2 mg of morphine in the body, only 1 mg (50% of 2 mg) will be lost in 3 hours. Note that, in both cases, morphine levels drop by 50% during an interval of one half-life, but the actual *amount* lost is larger when total body stores of the drug are higher.

The half-life of a drug determines the dosing interval (i.e., how much time separates each dose). For drugs with a short half-life, the dosing interval must be correspondingly short. If a long dosing interval were used, drug levels would fall below the MEC between doses, and therapeutic effects would be lost. Conversely, if a drug has a long half-life, a long time can separate doses without loss of benefits.

Drug Levels Produced With Repeated Doses

Multiple dosing leads to drug accumulation. When a patient takes a single dose of a drug, plasma levels simply go up, and then come back down. In contrast, when a patient takes repeated doses of a drug, the process is more complex and results in drug accumulation. The factors that determine the rate and extent of accumulation are considered in the following sections.

The Process by Which Plateau Drug Levels Are Achieved

Administering repeated doses will cause a drug to build up in the body until a *plateau* (steady level) has been achieved. What causes drug levels to reach plateau? If a second dose of a drug is administered before all of the prior dose has been eliminated, total body stores of that drug will be higher after the second dose than after the initial dose. As succeeding doses

are administered, drug levels will climb even higher. The drug will continue to accumulate until a state has been achieved in which the amount of drug eliminated between doses equals the amount administered. *When the amount of drug eliminated between doses equals the dose administered, average drug levels will remain constant and plateau will have been reached.*

The process by which multiple dosing produces a plateau is illustrated in Fig. 4.14. The drug in this figure is a hypothetical agent with a half-life of exactly 1 day. The regimen consists of a 2-gm dose administered once daily. For the purpose of illustration, we assume that absorption takes place instantly. Upon giving the first 2-gm dose (day 1 in the figure), total body stores go from zero to 2 gm. Within one half-life (1 day), body stores drop by 50%—from 2 gm down to 1 gm. At the beginning of day 2, the second 2-gm dose is given, causing body stores to rise from 1 gm up to 3 gm. Over the next day (one half-life), body stores again drop by 50%, this time from 3 gm down to 1.5 gm. When the third dose is given, body stores go from 1.5 gm up to 3.5 gm. Over the next half-life, stores drop by 50% down to 1.75 gm. When the fourth dose is given, drug levels climb to 3.75 gm and, between doses, levels again drop by 50%, this time to approximately 1.9 gm. When the fifth dose is given (at the beginning of day 5), drug levels go up to about 3.9 gm. This process of accumulation continues until body stores reach 4 gm. When total body stores of this drug are 4 gm, 2 gm will be lost each day (i.e., over one half-life). Because a 2-gm dose is being administered each day, when body stores reach 4 gm, the amount lost between doses will equal the dose administered. At this point, body stores will simply alternate between 4 gm and 2 gm; average body stores will be stable, and plateau will have been reached. Note that the reason that plateau is finally reached is that the actual amount of drug lost between doses gets larger each day. That is, although 50% of total body stores is lost each day, the *amount* in grams grows progressively larger because total body stores are getting larger day by day. Plateau is reached when the amount lost between doses grows to be as large as the amount administered.

Time to Plateau

When a drug is administered repeatedly in the same dose, *plateau will be reached in approximately four half-lives*. For the hypothetical agent illustrated in Fig. 4.14, total body stores approached their peak near the beginning of day 5, or approximately 4 full days after treatment began. Because the half-life of this drug is 1 day, reaching plateau in 4 days is equivalent to reaching plateau in four half-lives.

As long as dosage remains constant, the time required to reach plateau is independent of dosage size. Put another way, the time required to reach plateau when giving repeated large doses of a particular drug is identical to the time required to reach plateau when giving repeated small doses of that drug. Referring to the drug in Fig. 4.14, just as it took four half-lives (4 days) to reach plateau when a dose of 2 gm was administered daily, it would also take four half-lives to reach plateau if a dose of 4 gm were administered daily. It is true that the *height* of the plateau would be greater if a 4-gm dose were given, but the time required to reach plateau would not be altered by the increase in dosage. To confirm this statement, substitute a dose of 4 gm in the previous exercise and see when plateau is reached.

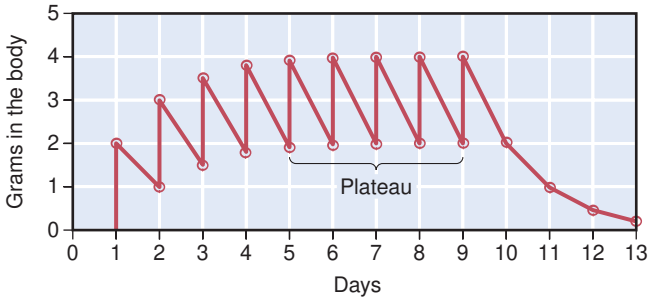

Fig. 4.14 ▪ Drug accumulation with repeated administration.
The drug has a half-life of 1 day. The dosing schedule is 2 gm given once a day on days 1 through 9. Note that plateau is reached at about the beginning of day 5 (i.e., after four half-lives). Note also that, when administration is discontinued, it takes about 4 days (four half-lives) for most (94%) of the drug to leave the body.

Techniques for Reducing Fluctuations in Drug Levels

As illustrated in Fig. 4.14, when a drug is administered repeatedly, its level will fluctuate between doses. The highest level is referred to as the *peak concentration*, and the lowest level is referred to as the *trough concentration*. The acceptable height of the peaks and troughs will depend on the drug's therapeutic range. The peaks must be kept below the toxic concentration, and the troughs must be kept above the MEC. If there is not much difference between the toxic concentration and the MEC, then fluctuations must be kept to a minimum.

Three techniques can be employed to reduce fluctuations in drug levels. One technique is to *administer drugs by continuous infusion*. With this procedure, plasma levels can be kept nearly constant. Another is to *administer a depot preparation*, which releases the drug slowly and steadily. The third is to *reduce both the size of each dose and the dosing interval* (keeping the total daily dose constant). For example, rather than giving the drug from Fig. 4.14 in 2-gm doses once every 24 hours, we could give this drug in 1-gm doses every 12 hours. With this altered dosing schedule, the total daily dose would remain unchanged, as would total body stores at plateau. Instead of fluctuating over a range of 2 gm between doses, however, levels would fluctuate over a range of 1 gm.

Loading Doses Versus Maintenance Doses

As discussed earlier, if we administer a drug in repeated doses of *equal size*, an interval equivalent to about four half-lives is required to achieve plateau. For drugs whose half-lives are long, achieving plateau could take days or even weeks. When plateau must be achieved more quickly, a large initial dose can be administered. This large initial dose is called a *loading dose*. After high drug levels have been established with a loading dose, plateau can be maintained by giving smaller doses. These smaller doses are referred to as *maintenance doses*.

The claim that use of a loading dose will shorten the time to plateau may appear to contradict an earlier statement, which said that the time to plateau is not affected by dosage size. Nevertheless, there is no contradiction. For any *specified dosage*, it will always take about four half-lives to reach plateau. When a loading dose is administered followed by maintenance doses, the plateau is not reached *for the loading dose*. Rather, we have simply used the loading dose to rapidly produce a

drug level equivalent to the plateau level for a smaller dose. To achieve plateau level for the loading dose, it would be necessary to either administer repeated doses equivalent to the loading dose for a period of four half-lives or administer a dose even larger than the original loading dose.

Decline From Plateau

When drug administration is discontinued, most (94%) of the drug in the body will be eliminated over an interval equal to about four half-lives. This statement can be validated with simple arithmetic. Let us consider a patient who has been taking morphine. In addition, let us assume that, at the time dosing ceased, the total body store of morphine was 40 mg. Within one half-life after drug withdrawal, morphine stores will decline by 50%—down to 20 mg. During the second half-life, stores will again decline by 50%, dropping from 20 mg to 10 mg. During the third half-life, the level will decline once more by 50%—from 10 mg down to 5 mg. During the fourth half-life, the level will again decline by 50%—from 5 mg down to 2.5 mg. Hence, over a period of four half-lives, total body stores of morphine will drop from an initial level of 40 mg down to 2.5 mg, an overall decline of 94%. Most of the drug in the body will be cleared within four half-lives.

The time required for drugs to leave the body is important when toxicity develops. Let us consider the elimination of digitoxin (a drug once used for heart failure). Digitoxin, true to its name, is a potentially dangerous drug with a narrow therapeutic range. In addition, the half-life of digitoxin is prolonged—about 7 days. What will be the consequence of digitoxin overdose? Toxic levels of the drug will remain in the body for a long time: Because digitoxin has a half-life of 7 days and because four half-lives are required for most of the drug to be cleared from the body, it could take weeks for digitoxin stores to fall to a safe level. During the time that excess drug remains in the body, significant effort will be required to keep the patient alive. If digitoxin had a shorter half-life, body stores would decline more rapidly, thereby making management of overdose less difficult. (Because of its long half-life and potential for toxicity, digitoxin has been replaced by digoxin, a drug with identical actions but a much shorter half-life.)

It is important to note that the concept of half-life does not apply to the elimination of all drugs. A few agents, most notably ethanol (alcohol), leave the body at a *constant rate*, regardless of how much is present. The implications of this kind of decline for ethanol are discussed in Chapter 41.

KEY POINTS

- Pharmacokinetics consists of four basic processes: absorption, distribution, metabolism, and excretion.
- Pharmacokinetic processes determine the concentration of a drug at its sites of action and thereby determine the intensity and time course of responses.
- To move around the body, drugs must cross membranes, either by (1) passing through pores, (2) undergoing transport, or (3) penetrating the membrane directly.
- P-glycoprotein—found in the liver, kidney, placenta, intestine, and brain capillaries—can transport a variety of drugs *out* of cells.
- To cross membranes, most drugs must dissolve directly into the lipid bilayer of the membrane. Accordingly, lipid-soluble drugs can cross membranes easily, whereas drugs that are polar or ionized cannot.
- Acidic drugs ionize in basic (alkaline) media, whereas basic drugs ionize in acidic media.
- Absorption is defined as the movement of a drug from its site of administration into the blood.
- Absorption is enhanced by rapid drug dissolution, high lipid solubility of the drug, a large surface area for absorption, and high blood flow at the site of administration.
- Intravenous administration has several advantages: rapid onset, precise control over the amount of drug entering the blood, suitability for use with large volumes of fluid, and suitability for irritant drugs.
- Intravenous administration has several disadvantages: high cost; difficulty; inconvenience; danger because of irreversibility; and the potential for fluid overload, infection, and embolism.
- Intramuscular administration has two advantages: suitability for insoluble drugs and suitability for depot preparations.
- Intramuscular administration has two disadvantages: inconvenience and the potential for discomfort.
- Subcutaneous administration has the same advantages and disadvantages as IM administration.
- Oral administration has the advantages of ease, convenience, economy, and safety.
- The principal disadvantages of oral administration are high variability and possible inactivation by stomach acid, digestive enzymes, and liver enzymes (because oral drugs must pass through the liver before reaching the general circulation).
- Enteric-coated oral formulations are designed to release their contents in the small intestine—not in the stomach.
- Sustained-release oral formulations are designed to release their contents slowly, thereby permitting a longer interval between doses.
- Distribution is defined as drug movement from the blood to the interstitial space of tissues, and from there into cells.
- In most tissues, drugs can easily leave the vasculature through spaces between the cells that compose the capillary wall.
- The term *blood-brain barrier* (BBB) refers to the presence of tight junctions between the cells that compose capillary walls in the CNS. Because of this barrier, drugs must pass through the cells of the capillary wall, rather than between them, to reach the CNS.
- The membranes of the placenta do not constitute an absolute barrier to the passage of drugs. The same factors that determine drug movements across all other membranes determine the movement of drugs across the placenta.
- Many drugs bind reversibly to plasma albumin. While bound to albumin, drug molecules cannot leave the vascular system.