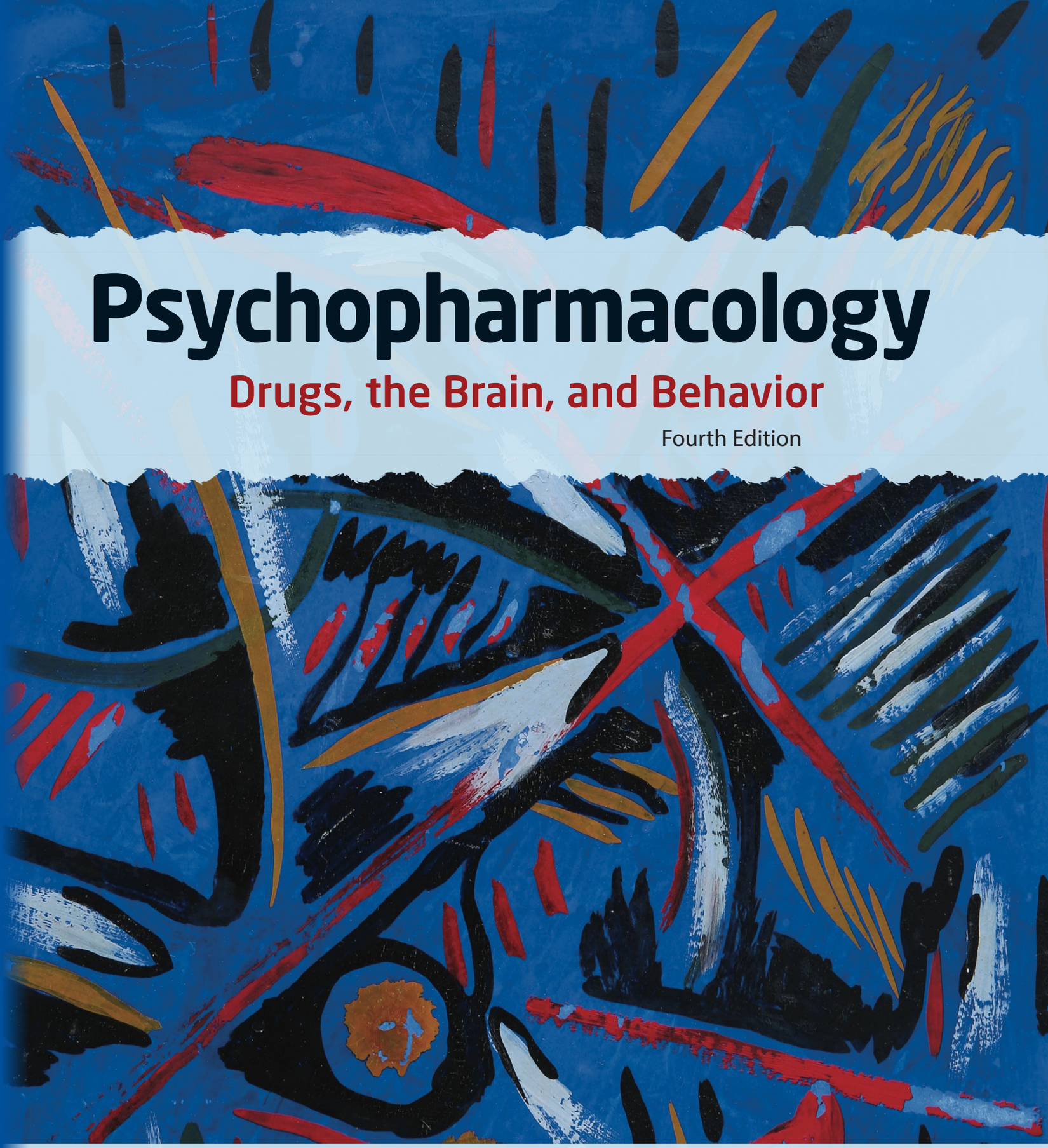

Psychopharmacology

Drugs, the Brain, and Behavior

Fourth Edition

Jerrold S. Meyer ▪ Andrew M. Farrar
Dominik Biezonski ▪ Jennifer R. Yates

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Brief Contents

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Preface

Jerrold Meyer and Linda Quenzer were approached by Sinauer Associates about 20 years ago to develop a new undergraduate textbook on psychopharmacology. We were already co-authors with Robert Feldman on a massive, 900-page-long graduate level textbook entitled *Principles of Neuropsychopharmacology*, but our Sinauer editor wanted something more than just a condensed and simplified version of the "big book." Our charge was to engage the interest of undergraduate students in learning about psychoactive drugs and their mechanisms of action, while maintaining the more advanced textbook's high standard of comprehensive and up-to-date coverage. The fact that Sinauer has now published the Fourth Edition of *Psychopharmacology: Drugs, the Brain, and Behavior,* indicates that we have had some success in fulfilling that charge.

In the preface to the first edition of this work, the authors commented on the long history of human use of mind-altering substances that eventually led to the need for a science of psychopharmacology. This field of study was already exploding by the late 20th and early 21st centuries, and nothing has happened since then to slow down this remarkable growth. However, new trends are always emerging in any vibrant area of scholarship, and psychopharmacology is no exception in that regard. One such trend particularly worth noting is the impact of changing attitudes toward formerly disparaged substances, at least within Western societies. This impact can be seen in two significant developments. First, many countries or smaller political districts (i.e., states, provinces, or cities), especially within North America and Western Europe, are decriminalizing the personal use of various recreational drugs. Some drugs, like cannabis, have even been fully legalized for such use. Although the politics of decriminalization and legalization remain contentious, a clear trend is in place. Second, we are seeing a remarkable development of therapeutic applications using mind-altering drugs like psilocybin, LSD, MDMA (ecstasy), and ketamine, that until recently were deemed highly addictive and (except for ketamine) without legitimate medical use. Again, this development is not without controversy; however, we are convinced that the growing empirical evidence for therapeutic benefits derived from careful use of psychedelic medications will cement their place in the therapeutic domain.

In accordance with pharmacology being a medical discipline, this new edition continues to emphasize the known or potential therapeutic applications of every compound mentioned in the textbook. However, it's important for readers to recognize not only the advances being made in medications development for some CNS disorders, but also the areas where progress has been frustratingly slow. For example, the introduction of new and exciting psychedelic medications promises to benefit mood-, anxiety-, and trauma-related disorders, but these drugs are less likely to help patients recover from neurodegenerative disorders like Alzheimer's disease, multiple sclerosis, or amyotrophic lateral sclerosis. Drug addiction and autism spectrum disorders are two other important areas where advances in pharmacotherapy have lagged. Therefore, throughout the book we have tried to identify the specific therapeutic benefits and limitations (where appropriate) of each successful medication, failures of medications that seemed promising at one time, and gaps where new medications are sorely needed.

Every chapter in this Fourth Edition is fully updated, with many citations from 2020 and 2021. Special attention is given to recent developments and emerging trends in psychopharmacology while retaining the same organization as in previous editions. The first four chapters provide extensive foundation materials, including the basic principles of pharmacology, neurophysiology and neuroanatomy, cell signaling in the nervous and endocrine systems, and current methods in behavioral assessment and neuropharmacology. The new Case Studies box feature is used in Chapter 1 (Principles of Pharmacology) and in Chapter 2 (Structure and Function of the Nervous System) to demonstrate how the basic concepts of pharmacology and neuroscience are applied in clinical practice. Among the highlights of Chapter 3 (Chemical Signaling by Neurotransmitters and Hormones) are expanded coverage of oxytocin and vasopressin regulation of social behaviors and current evidence on the use of oxytocin to treat the social communication deficits present in autism spectrum disorder. Chapter 4 (Methods of Research in Psychopharmacology) is updated with examples of state-of-the-art techniques, including examples from genetic engineering and artificial intelligence, to illustrate how these technologies are being used to better understand drug effects on behavior and the complex

genetic basis of drug-organism interactions. The next four chapters, Chapter 5 (Catecholamines), Chapter 6 (Serotonin), Chapter 7 (Acetylcholine), and Chapter 8 (Glutamate and GABA), describe the key features of neurotransmitter systems that are particularly important to psychopharmacologists. Information about the neurochemistry, anatomy, and behavioral functions of these transmitters not only lays the groundwork for the chapters that follow, but this new edition places increased emphasis on clinical applications of neurotransmitter-targeted drugs. The next eight chapters focus on recreational drugs and their potential for misuse. Chapter 9 (Drug Misuse and Addiction) covers the current theories and mechanisms of drug addiction, which is followed by seven chapters devoted to specific recreational drugs. Chapter 10 (Alcohol) discusses the pharmacology of alcohol, the features of alcohol use disorder (previously called alcoholism), and both current and emerging treatments for this disorder. Chapter 11 (The Opioids) describes the features of the endogenous opioid system, opioid use disorder, and novel treatments for that disorder. The chapter has been updated to reflect the increasing severity of the opioid epidemic and the array of harm-reduction strategies being employed to combat it. This section of the book continues with Chapter 12 (Psychomotor Stimulants: Cocaine, Amphetamine, and Related Drugs), Chapter 13 (Nicotine and Caffeine), Chapter 14 (Marijuana and the Cannabinoids), Chapter 15 (Psychedelic and Hallucinogenic Drugs, PCP, and Ketamine), and Chapter 16 (Inhalants, GHB, and Anabolic-Androgenic Steroids). Among the highlights of these chapters are greatly expanded coverage of e-cigarettes and vaping (Chapter 13), new discussions of cannabis legalization and emerging therapeutic applications of cannabidiol (CBD) and other cannabinoids (Chapter 14), and the mechanisms by which entactogens and psychedelic drugs (MDMA, psilocybin, and LSD) are thought to work when used in drug-assisted psychotherapy for mood- and trauma-related disorders (Chapter 15). The final four chapters consider the neurobiology of neuropsychiatric and neurodegenerative disorders and the drugs used to treat these disorders. Chapter 17 (Disorders of Anxiety and Impulsivity and the Drugs Used to Treat Them) and Chapter 18 (Affective Disorders: Antidepressants and Mood Stabilizers) cover not only classical pharmacotherapies such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) but also novel approaches using more "non-traditional" substances such as ketamine and psilocybin, that are discussed in prior chapters on recreational drugs. We highlight ongoing studies on these substances that seek to determine optimal dosing regimens, tolerability, durability, and mechanisms of action, the latter which may lead to the generation of novel compounds with reduced side effects. Chapter 19 (Schizophrenia: Antipsychotic Drugs) has been updated with examples of recent studies demonstrating the promise of pharmacogenetics in optimizing treatment efficacy while reducing side effects, such as tardive dyskinesia. Finally, Chapter 20 (Neurodegenerative Diseases) updates our discussion of the symptoms, clinical trials, FDA-approved therapies, and diagnostic tools, including advances in neuroimaging, for all disorders covered in the chapter. It additionally introduces novel developments such as a new symptom (unusual body odor) that helps diagnose Parkinson's disease and a recently developed technology (focused ultrasound) for treating Alzheimer's disease.

Several features of *Psychopharmacology: Drugs, the Brain, and Behavior* distinguish it from its many competitors. Full-color photos depict pharmacologically relevant plant species, drugs in crystalline form, and drug-related paraphernalia. Beautifully rendered four-color illustrations present data from important experiments and portray models of drug action, including neural pathways thought to mediate the psychological and behavioral effects of specific substances. Bulleted interim summaries highlight the key points made in each part of the chapter, and study questions are provided at the end of each chapter to assist students in reviewing the most important material. A new feature for this edition is the inclusion of learning objectives at the beginning of each section to help direct students and instructors towards the main content to be covered. Breakout boxes (printed and on the web) categorized by the themes of Pharmacology in Action, The Cutting Edge, Of Special Interest, Clinical Applications, Case Studies, and History of Psychopharmacology highlight topics of particular importance. Finally, the new Enhanced e-book offers access to Web Boxes, study resources such as self assessment at the end of each section, flashcards, weblinks and animations that visually illustrate key neurophysiological and neurochemical processes important for Psychopharmacology.

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Readers familiar with previous editions of this textbook may notice that the long-standing co-author Linda Quenzer was not involved in preparing this new edition. Although Linda has retired from textbook writing, she has been ably replaced by new co-authors Andrew Farrar and Dominik Biezonski. We are confident that this new team, which includes previous contributor Jennifer Yates, has produced a worthy successor to previous editions of the textbook. We hope that you, the reader, will ultimately agree with that assessment.

Acknowledgments

This book is the culmination of the efforts of many dedicated people who contributed their ideas and hard work to the project. We'd like to thank and acknowledge the outstanding editorial team at Sinauer Associates/Oxford University Press: Jessica Fiorillo (Executive Editor), Johannah Walkowicz (Production Editor), and Malinda Labriola (Editorial Assistant). Thank you all for your help in putting together the Fourth Edition, your guidance in making the transition to Oxford University Press, and not least your patience throughout the process of writing, revising, and revising again when necessary. You had a vision for this project that kept us moving forward in our goal of producing the best possible psychopharmacology textbook. Mark Siddall continues to do a fantastic job of seeking out just the right photographs for the book. We are indebted to other key staff members of Oxford University Press who worked on this project, including Joan Gemme, Meg Britton Clark, Michele Beckta, Suzanne Carter, and Sean Hynd. We also thank Wendy Walker and Danna Lockwood for their help with editing, and Melissa Flamson for assisting with permissions. And we must acknowledge Dragonfly Media Group for the beautiful job rendering the illustrations.

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Lastly, we would like to acknowledge and thank the many adopters of this textbook and their students. To new adopters, we appreciate your selection and trust that you will still be happy with that selection after having used the book in your classroom. If you are a previous adopter, we thank you for your continued loyalty that has made it possible to reach this Fourth Edition of the book. Finally, if you are a student, we hope that reading our book and studying the field of psychopharmacology might inspire you to choose this exciting and dynamic field for your own career so that in the years to come, your name might be among the researchers cited in a future edition of *Psychopharmacology: Drugs, the Brain, and Behavior.*

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Enhanced E-Book for the Student

(ISBN 9781605359892)

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The Web Boxes are also available to students using the print book. Go to **oup.com/he/meyer4e**.

1 Principles of Pharmacology

WILLIAM S. BAER (1872–1931) WAS AN ORTHOPEDIC SURGEON at Johns Hopkins University, where he established the orthopedic department and led it for most of his life, training many of the outstanding orthopedists of the day. During World War I Baer observed that soldiers who had severe and deep flesh wounds did not have the fever associated with infection and showed little of the expected necrotic (dead) tissue damage if there was a significant presence of maggots (fly larvae) in the wounds. Although it had been believed that early peoples (Australian aborigines and Mayan Indian tribes) and others throughout history had used maggots to clean wounds, it was Baer who once again recognized their importance, especially in tense battlefield conditions where infection was especially hard to treat. Apparently the maggots ingested the dying tissue but left healthy tissue intact. Baer, upon doing further "pharmacological" experiments, showed that his hospitalized patients with severe and chronic bone infections showed remarkable recovery after being treated with maggots—the inflamed and dying tissue was ingested, leaving wounds clean and healthy, and new tissue formed. As long as the maggots were sterilized, secondary infections were avoided. After his research, "maggot therapy" became popular and was used throughout the 1930s and 1940s until penicillin was established as an easier treatment for infection. However, it has been suggested that in modern times, maggot therapy will be reintroduced to treat those wounds infected with antibiotic-resistant bacteria. At present in the European Union, Japan, and Canada, maggots are considered "medicinal drugs," and in 2005 the U.S. Food and Drug Administration approved the use of maggots as a medical "device."

What actually causes the amazing healing process is not entirely clear, but pharmacologists are beginning to understand that maggot secretions suppress the immune system and reduce inflammation, and they may also enhance cell growth and increase oxygen concentration in the wound. This is certainly not the first time pharmacology has returned to earlier forms of therapeutics, but the science now can isolate and identify those components that lead to healing. ■

Maggot therapy can be used to clean wounds and prevent infection.

1.1 Pharmacology: The Science of Drug Action

Pharmacology is the scientific study of the actions of drugs and their effects on a living organism. Until the beginning of the last century, pharmacologists studied drugs that were almost all naturally occurring substances. The importance of plants in the lives of ancient humans is well documented. Writings from as early as 1500 BCE describe plant-based medicines used in Egypt and in India. The Ebers Papyrus describes the preparation and use of more than 700 remedies for ailments as varied as crocodile bites, baldness, constipation, headache, and heart disease. Of course, many of these treatments included elements of magic and incantation, but there are also references to some modern drugs such as castor oil and opium. The Chinese also have a very long and extensive tradition in the use of herbal remedies that continues today. World Health Organization estimates suggest that in modern times, as many as 80% of the people in developing countries are totally dependent on herbs or plant-derived medicinals. And in 1999, in the United States, modern herbal medicines and drugs based on natural products represented half of the top 20 drugs on the market (Hollinger, 2008). Many Americans are enamored with herbal medications despite limited clinical support for their effectiveness, because they believe these treatments are more "natural." Nevertheless, serious dangers have been associated with some of them. **WEB BOX 1.1** discusses the benefits and dangers of herbal remedies.

When placed in historical context, it can be seen that drug development in the United States is in its infancy. The rapid introduction of many new drugs by the pharmaceutical industry has forced the development of several specialized areas of pharmacology. Two of these areas are of particular interest to us. **Neuropharmacology** is concerned with drug-induced changes in the functioning of cells in the nervous system, and **psychopharmacology** emphasizes drug-induced changes in mood, thinking, and behavior. In combination, the goal of **neuropsychopharmacology** is to identify chemical substances that act on the nervous system to alter behavior that is disturbed because of injury, disease, or environmental factors. Additionally, neuropsychopharmacologists are interested in using chemical agents as probes to gain an understanding of the neurobiology of behavior.

When we speak of **drug action**, we are referring to the specific molecular changes produced by a drug when it binds to a particular target site or receptor. These molecular changes lead to more widespread alterations in physiological or psychological functions, which we consider **drug effects**. The site of drug action may be very different from the site of drug effect. For example, atropine is a drug used in ophthalmology to dilate the pupil of the eye before eye examinations. Atropine has a site of action (the eye muscles of the iris) that is close to the site of its ultimate effect (widening the pupil), so it is administered directly to the eye. In comparison, morphine applied to the eye itself has no effect. Yet when it is taken internally, the drug's action on the brain leads to "pinpoint" pupils. Clearly, for morphine, the site of effect is far distant from the site of its initial action.

Keep in mind that because drugs act at a variety of target sites, they always have multiple effects. Some may be **therapeutic effects**, meaning that the drug–receptor interaction produces desired physical or behavioral changes. All other effects produced are referred to as **side effects**, and they vary in severity from mildly annoying to distressing and dangerous. For example, amphetamine-like drugs produce alertness and insomnia, increased heart rate, and decreased appetite. Drugs in this class reduce the occurrence of spontaneous sleep episodes characteristic of the disorder called *narcolepsy*, but they produce anorexia (loss of appetite) as the primary side effect. In contrast, the same drug may be used as a prescription diet control in weight-reduction programs. In such cases, insomnia and hyperactivity are frequently disturbing side effects. Thus therapeutic and side effects can change, depending on the desired outcome.

It is important to keep in mind that there are no "good" or "bad" drugs, because all drugs are just chemicals. It is the way a drug is procured and used that determines its character. Society tends to think of "good" drugs as those purchased at a pharmacy and taken at the appropriate dosage for a particular medicinal purpose, and "bad" drugs as those acquired in an illicit fashion and taken recreationally to achieve a desired psychological state. Even with this categorization, the differences are blurred because many people consider alcohol to be "bad" even though it is purchased legally. Morphine and cocaine have legitimate medicinal uses, making them "good" drugs under some conditions, although they can, when misused, lead to dangerous consequences and addiction, making the same drugs "bad." Finally, many "good" prescription drugs are acquired illicitly or are misused by increasing the dose, prolonging use, or sharing the drug with other individuals, leading to "bad" outcomes. As you will read in later chapters, the ideas of Americans about appropriate drug use have changed dramatically over time (see the sections on the history of the use of narcotics in Chapter 11 and cocaine in Chapter 12).

Many of the drug effects we have described so far have been **specific drug effects**, defined as those based on the physical and biochemical interactions of a drug with a target site in living tissue. In contrast, **nonspecific drug effects** are those that are based not on the chemical activity of a drug–receptor interaction, but on certain unique characteristics of the individual. It is clear that an individual's background (e.g., drug-taking

experience), present mood, expectations of drug effect, perceptions of the drug-taking situation, attitude toward the person administering the drug, and other factors influence the outcome of drug use. Nonspecific drug effects help to explain why the same individual self-administering the same amount of ethyl alcohol may experience a sense of being lighthearted and gregarious on one occasion, and depressed and melancholy on another. The basis for such a phenomenon may well be the varied neurochemical states existing within the individual at different times, with which specific drug effects interact.

Placebo effect

Common examples of nonspecific effects are the multiple outcomes that result from taking a **placebo**. Many of you automatically think of a placebo as a "fake" pill. A placebo *is* in fact a pharmacologically inert compound administered to an individual; however, in many instances it has not only therapeutic effects, but side effects as well. Just as many of the symptoms of illness may have psychogenic or emotional origins, belief in a drug may produce real physiological effects despite the lack of chemical activity. These effects are not limited to the individual's subjective evaluation of relief but include measurable physiological changes such as altered gastric acid secretion, blood vessel dilation, hormonal changes, and so forth.

In a classic study, two groups of patients with ulcers were given a placebo. In the first group, the medication was provided by a physician, who assured the patients that the drug would provide relief. The second group also received the placebo, but it was administered by a nurse, who described it as experimental in nature. In group 1, 70% of the patients found significant relief, but in group 2, only 25% were helped by the "drug" (Levine, 1973). Based on these results, it is clear that a sugar pill is not a drug that can heal ulcers, but rather its effectiveness depends on the ritual of the therapeutic treatment that can have both neurobiological and behavioral effects that influence the outcome. It is a perfect example of mind–body interaction, and there has been increasing interest in understanding the mechanism responsible for the placebo effect as a means to enhance the therapeutic effectiveness of drug treatments. Although some consider deliberate prescription of placebos to patients unethical because of the deception involved, other physicians and ethicists have identified appropriate uses for placebos that represent an inexpensive treatment that avoids unnecessary medications.

Placebo effects may in part be explained by Pavlovian conditioning in which symptom improvement in the past has been associated with particular characteristics of a medication, for example its taste, color, shape, and size; a particular recommending clinician, with her white coat, reassuring tone of voice, or attitude; or aspects of the medical facility. Since a placebo effect has been demonstrated many times in animal models, cues in the environment are apparently sufficient, and verbal reassurances are not necessary. In fact, patients have been shown to benefit even if they are told that the medication is a placebo, so deception is apparently not a necessity; however, verbal suggestion interacts with conditioning (see Colagiuri et al., 2015).

A second possible explanation for the placebo effect is that of conscious, explicit expectation of outcomes. For example, those individuals who anticipate relief may show an enhanced placebo response. Of great interest are the placebo-induced neurobiological effects within the brain. Research has shown that when placebos effectively reduce pain, those individuals who are responders have significantly higher levels of natural pain-relieving opioid neuropeptides in their cerebrospinal fluid than those individuals who do not show a response to the placebo. Further, the subjects who anticipate pain relief show reduced neural activity in pain-related brain regions (see Benedetti et al., 2011).

While Pavlovian conditioning and conscious expectation both contribute to the placebo effect, other factors may also have a part (see Murray and Stoessl, 2013; Carlino et al., 2016). Placebo effects may involve social learning. That is, observing another individual anticipating a positive outcome can be a more powerful inducer of the placebo effect than direct conditioning or verbal suggestions. Others have found that anticipating a successful outcome reduces anxiety and activates reward networks in the brain. Finally, a number of genetic variants have been found that influence the placebo effect. Understanding more about which genes identify patients who will respond to placebo could allow treatment to be adjusted to maximize outcome (Colagiuri et al., 2015). This is one step toward personalized medicine (see the last section of this chapter).

In contrast to placebos, negative expectations may increase the level of anxiety experienced, which may also influence the outcome of treatment. Expecting treatment failure when an inert substance is given along with verbal suggestions of negative outcome, such as increased pain or another aversive event, would increase anxiety as well as cause an accompanying change in neural mechanisms, including increases in stress hormones. This is the **nocebo** effect, and both the nocebo-induced increase in pain reported and the hormonal stress response can be reduced by treatment with an antianxiety drug, demonstrating that expectation-induced anxiety plays a part in the nocebo effect. Nocebos are important to study because warnings about potential side effects can lead to greater side-effect occurrence. Unfortunately, because drug companies are required by law to provide a comprehensive listing of all possible side effects, many individuals have negative expectations, leading to increased side effects.

BOX 1.1 ■ PHARMACOLOGY IN ACTION

Naming Drugs

Drug names can be a confusing issue for many people because drugs that are sold commercially, by prescription or over the counter, usually have four or more different kinds of names.

All drugs have a *chemical name* that is a complete chemical description suitable for synthesizing by an organic chemist. Chemical names are rather clumsy and are rarely used except in a laboratory setting. In contrast, *generic* or *nonproprietary names* are official names of drugs that are listed in the United States Pharmacopeia. The generic name is a much shorter form of the chemical name but is still unique to that drug. For example, one popular antianxiety drug has the chemical name 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and the generic name diazepam. The *brand name*, or *trade name*, of that drug (Valium) specifies a particular manufacturer and a formulation. A brand name is trademarked and copyrighted by an individual company, which means that the company has an exclusive right to advertise and sell that drug.

Slang or *street names* of commonly abused drugs are another way to identify a particular chemical. Unfortunately, these names change over time and vary with geographical location and particular groups of people. In addition, there is no way to know the chemical characteristics of the substance in question. Some terms are used in popular films or television and become more generally familiar, such as "crack" or "ice," but most disappear as quickly as they appear.

In pharmacology, the placebo is essential in the design of experiments conducted to evaluate the effectiveness of new medications, because it eliminates the influence of expectation on the part of the experiment's participants. The control group is identical to the experimental group in all ways and is unaware of the substitution of an inactive substance (e.g., sugar pill, saline injection) for the test medication. Comparison of the two groups provides information on the effectiveness of the drug beyond the expectations of the participants. Of course, drugs with strong subjective effects or prominent side effects make placebo testing more challenging because the experimental group will be aware of the effects while those experiencing no effects will conclude they are the control group. To avoid that problem, some researchers may use an "active" placebo, which is a drug (unrelated to the drug being tested) that produces some side effects that suggest to the control participants that they are getting the active agent. In other cases clinical researchers may feel that it is unethical to leave the placebo group untreated if there is an effective agent available. In that case the control group will be given the older drug, and effectiveness of the new drug will be compared with it rather than with a placebo.

The large contribution of nonspecific factors and the high and variable incidence of placebo responders make the **double-blind experiment** highly desirable. In these experiments, neither the patient nor the observer knows what treatment the participant has received. Such precautions ensure that the results of any given treatment will not be biased on the part of the participant or the observer. If you would like to read more about the use of placebos in both clinical research and therapeutics and the associated ethical dilemmas, refer to the articles by Brown (1998) and Louhiala (2009).

Throughout this chapter, we present examples that include both therapeutic and recreational drugs that affect mood and behavior. Since there are usually several names for the same substance, it may be helpful for you to understand how drugs are named (**BOX 1.1**).

Pharmacokinetic factors determining drug action

Although it is safe to assume that the chemical structure of a drug determines its action, it quickly becomes clear that additional factors are also powerful contributors. The dose of the drug administered is clearly important, but more important is the amount of drug in the blood that is free to bind at specific target sites (**bioavailability**) to elicit drug action. The following sections of this chapter describe in detail the dynamic factors that contribute to bioavailability. Collectively, these factors constitute the **pharmacokinetic** component of drug action; they are listed below and illustrated in **FIGURE 1.1**.

1. *Routes of administration*. How and where a drug is administered determines how quickly and how completely the drug is absorbed into the blood.
2. *Absorption and distribution*. Because a drug rarely acts where it initially contacts the body, it must pass through a variety of cell membranes and enter the blood plasma, which transports the drug to virtually all of the cells in the body.
3. *Binding*. Once in the blood plasma, some drug molecules move to tissues to bind to active target sites (receptors). While in the blood, a drug may

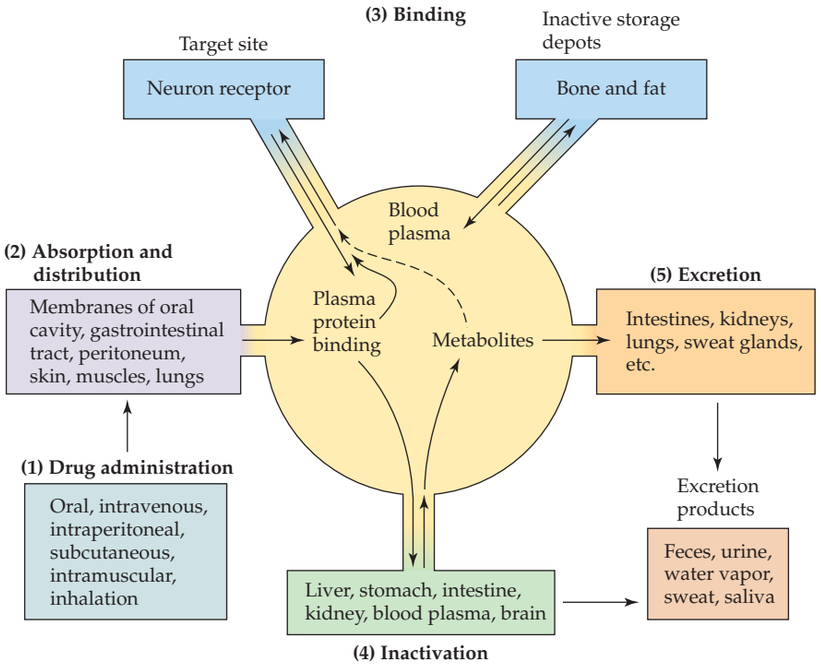

FIGURE 1.1 Pharmacokinetic factors that determine bioavailability of drugs From the site of administration (1), the drug moves through cell membranes to be absorbed into the blood (2), where it circulates to all cells in the body. Some of the drug molecules may bind to inactive sites such as plasma proteins or storage depots (3), and others may bind to receptors in target tissue. Bloodborne drug molecules also enter the liver (4), where they may be transformed into metabolites and travel to the kidneys and other discharge sites for ultimate excretion (5) from the body.

also bind (**depot binding**) to plasma proteins or may be stored temporarily in bone or fat, where it is inactive.

4. *Inactivation*. Drug inactivation, or **biotransformation**, occurs primarily as a result of metabolic processes in the liver as well as other organs and tissues. The amount of drug in the body at any one time is dependent on the dynamic balance between absorption and inactivation. Therefore, inactivation influences both the intensity and the duration of drug effects.
5. *Excretion*. The drug metabolites are eliminated from the body with the urine or feces. Some drugs are excreted in an unaltered form by the kidneys.

Although these topics are discussed sequentially in the following pages, keep in mind that in the living organism, these factors are at work simultaneously. In addition to bioavailability, the drug effect experienced will also depend on how rapidly the drug reaches its target, the frequency and history of prior drug use (see the discussion on tolerance later in the chapter), and nonspecific factors that are characteristics of individuals and their environments.

Methods of drug administration influence the onset of drug action

The route of administration of a drug determines how much drug reaches its site of action and how quickly the drug effect occurs. There are two major categories of administration methods. **Systemic** routes of administration refer to methods in which drugs distribute throughout the entire body, thus reaching the target tissue through general circulation. Within the broad category of systemic administration, **enteral** methods of administration use the gastrointestinal (GI) tract (*enteron* is the Greek word for "gut"); agents administered by these methods are generally slow in onset and produce highly variable blood levels of drug. The most common enteral method of administration is oral, but rectal administration with the use of suppositories is another enteral route. Other systemic routes of administration are **parenteral** and include those that do not use the alimentary canal, such as injection or pulmonary administration.

Oral administration (**PO**) is the most commonly used route for taking drugs, because it is safe, self-administered, and economical, and it avoids the complications and discomfort of injection methods. Drugs that are taken orally come in the form of capsules, pills, tablets, or liquid, but to be effective, the drug must dissolve in stomach fluids and pass through the stomach or intestine wall to reach blood capillaries. In addition, the drug must be resistant to destruction by stomach acid and stomach enzymes that are important for normal digestion.

Movement of the drug from the site of administration to the blood circulation is called **absorption**. Although some drugs are absorbed from the stomach, most drugs are not fully absorbed until they reach the small intestine. Many factors influence how quickly the stomach empties its contents into the small intestine and hence determine the ultimate rate of absorption. For example, food in the stomach, particularly if it is fatty, slows the movement of the drug into the intestine, thereby delaying absorption into the blood. The amount of food consumed, the level of physical activity of the individual, and many other factors

make it difficult to predict how quickly the drug will reach the intestine. In addition, many drugs undergo extensive first-pass metabolism. **First-pass metabolism** is an evolutionarily beneficial function because potentially harmful chemicals and toxins that are ingested pass via the portal vein to the liver, where they are chemically altered by a variety of enzymes before passing to the heart for circulation throughout the body (**FIGURE 1.2**). Unfortunately, some therapeutic drugs taken orally may undergo extensive metabolism (more than 90%), reducing their bioavailability. Drugs that show extensive first-pass effects must be administered at higher doses or in an alternative manner, such as by injection. Because of these many factors, oral administration produces drug plasma levels that are more irregular and unpredictable and rise more slowly than those produced by other methods of administration.

Rectal administration requires the placement of a drug-filled suppository in the rectum, where the suppository coating gradually melts or dissolves, releasing the drug, which will be absorbed into the blood. Depending on the placement of the suppository, the drug may avoid some first-pass metabolism. Drug absorbed from the lower rectum into the hemorrhoidal vein bypasses the liver. However, deeper placement means that the drug is absorbed by veins that drain into the portal vein, going to the liver before the general circulation. Bioavailability of drugs administered in this way is difficult to predict, because absorption is irregular (**BOX 1.2**). Although rectal administration is not used as commonly as oral administration, it is an effective

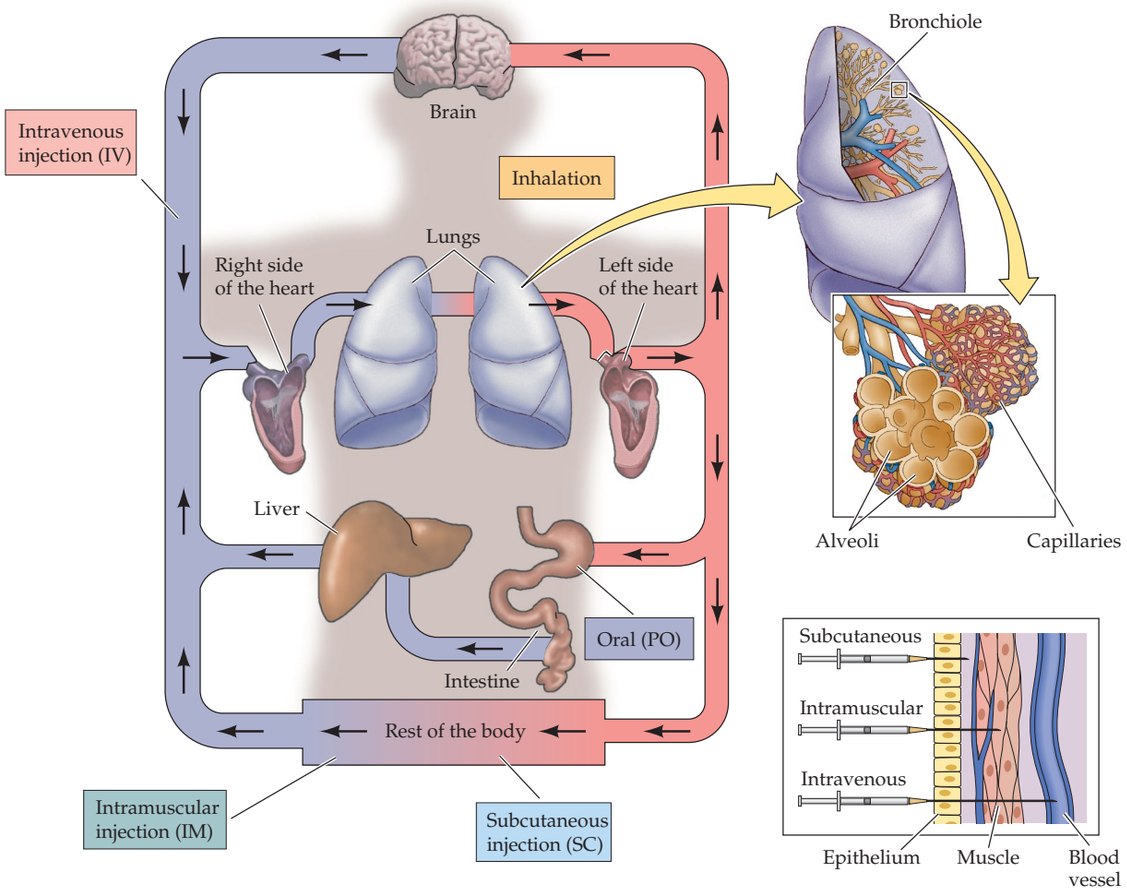

FIGURE 1.2 **Routes of drug administration** First-pass effect. Drugs administered orally are absorbed into the blood and must pass through the liver before reaching the general circulation. Some drug molecules may be destroyed in the liver before they can reach target tissues. The arrows indicate the direction of blood flow in the arteries (red) and veins (blue). (Top inset) Pulmonary absorption through capillaries in the alveoli. Rapid absorption occurs after inhalation because the large surface area of the lungs and the rich capillary networks provide efficient exchange of gases to and from the blood. (Bottom inset) Methods of administration by injection. The speed of absorption of drug molecules from administration sites depends on the amount of blood circulating to that area.

route in infants and in individuals who are vomiting, unconscious, or unable to take medication orally.

Intravenous (**IV**) injection is the most rapid and accurate method of drug administration in that a precise quantity of the agent is placed directly into the blood and passage through barriers such as the stomach wall is eliminated (see Figure 1.2). However, the quick onset of drug effect with IV injection is also a potential hazard. An overdose or a dangerous allergic reaction to the drug leaves little time for corrective measures, and the drug cannot be removed from the body as it can be removed from the stomach by stomach pumping.

For drug abusers, IV administration provides a more dramatic subjective drug experience than self-administration in other ways, because the drug reaches the brain almost instantly. Drug users report that intravenous injection of a cocaine solution usually produces an intense "rush" or "flash" of pure pleasure that lasts for approximately 10 minutes. This experience rarely occurs when cocaine is taken orally or is taken into the nostrils (snorting; see the discussion on topical administration). However, IV use of street drugs poses several special hazards. First, drugs that are impure or of unknown quality provide uncertain doses, and toxic reactions are common. Second, lack of sterile injection equipment and aseptic technique can lead to infections such as hepatitis, human immunodeficiency virus (HIV), and endocarditis (inflammation of the lining of the heart). Fortunately, many cities have implemented free needle programs, which significantly reduce the

BOX 1.2 ■ CASE STUDIES

The Perils of Alcohol Taken by an Unconventional Route of Administration

As described in this chapter, pharmacokinetic factors play a significant role in drug bioavailability and hence drug effects. With respect to drugs of abuse, many drug users experiment with alternative routes of administration in order to avoid unpleasant side effects or enhance the desired effects of a given drug. Ethyl alcohol, or ethanol, is consumed almost exclusively orally, in the form of a fermented drink, like beer or wine, or as a distilled spirit, like vodka or whiskey. When consumed by the oral route of administration, ethanol has relatively high bioavailability. However, because most ethanol is absorbed in the intestines, the stomach contents, and thus the rate of gastric emptying, can powerfully influence ethanol absorption and bioavailability.

Even though nearly all ethanol is consumed orally, even in cases of excessive consumption and abuse, some individuals have engaged in the dangerous practice of administering ethanol-containing drinks rectally, as an alcohol enema. The practice of rectally administering alcohol is highly risky for a couple of notable reasons. Alcohol, particularly at higher concentrations, is highly irritating to the sensitive mucosa of the colon, and as such, exposure to alcohol-containing drinks has resulted in numerous cases of severe colitis, requiring hospitalization. More seriously, the colon absorbs alcohol very rapidly, and unlike the stomach, the colon does not contain alcohol dehydrogenase (ADH), which normally begins the biotransformation of ethanol in the stomach before it is absorbed into the bloodstream. Moreover, ethanol absorbed through the colon does not undergo first-pass metabolism, further contributing to its elevated bioavailability. The more rapid absorption and hence higher bioavailability of ethanol through rectal administration can result in a blood-alcohol concentration that is significantly higher than if the same amount of ethanol were consumed orally. The higher bioavailability and thus more pronounced intoxicating effect of alcohol is likely chief among the reasons that some individuals choose to administer alcohol rectally. Other reasons may include avoidance of vomiting as well as the false belief that rectally administered alcohol would be undetectable on the breath.

Peterson and colleagues (2014) present the case of a 52-year-old man who was found deceased in his home following rectal administration of wine. At the time of autopsy, the decedent's blood-alcohol concentration was 350 mg/dL, while the vitreous ethanol concentration was 410 mg/dL. Determining postmortem alcohol content from the vitreous fluid of the eye is thought to reflect alcohol concentration more accurately at the time of death, since blood levels of alcohol tend to vary quite widely and decrease in the postmortem period. In any event, it is likely that the blood-alcohol concentration in the decedent was at least in the range of 350 to 410 mg/dL at the time of death, which is well within the range at which most people would suffer the fatal effects of ethanol.

While accidental ethanol overdoses resulting in death are relatively common, it is unusual that these fatal overdoses are the result of rectal administration. Given the high bioavailability of ethanol from this route of administration and hence the elevated potential for unintentional overdose, the small number of fatal overdoses likely reflects the fact that while dangerous, alcohol enema is a far less commonly used method of administration than oral consumption. As discussed in Chapter 10, alcohol overdose by any route of administration represents a fraction of the total number of alcohol-related fatalities, which can include fatalities caused by other dangerous behaviors, including motor vehicle accidents.

probability of cross-infection. Third, many drug abusers attempt to dissolve drugs that have insoluble filler materials, which, when injected, may become trapped in the small blood vessels in the lungs, leading to reduced respiratory capacity or death.

An alternative to the IV procedure is **intramuscular** (**IM**) injection, which provides the advantage of slower, more even absorption over a period of time. Drugs administered by this method are usually absorbed within 10 to 30 minutes. Absorption can be slowed down by combining the drug with a second drug that constricts blood vessels, because the rate of drug absorption is dependent on the rate of blood flow to the muscle (see Figure 1.2). To provide slower, sustained action, the drug may be injected as a suspension in vegetable oil. For example, IM injection of medroxyprogesterone acetate (Depo-Provera) provides effective contraception for 3 to 6 months without the need to take daily pills. One disadvantage of IM administration is that in some cases, the injection solution can be highly irritating, causing significant muscle discomfort.

Intraperitoneal (**IP**) injection is rarely used with humans, but it is the most common route of administration for small laboratory animals. The drug is injected through the abdominal wall into the peritoneal cavity—the space that surrounds the abdominal organs. IP injection produces rapid effects, but not as rapid as those produced by IV injection. Variability in absorption occurs, depending on where (within the peritoneum) the drug is placed.

In **subcutaneous** (**SC**) administration, the drug is injected just below the skin (see Figure 1.2) and is absorbed at a rate that is dependent on blood flow to the site. Absorption is usually fairly slow and steady, but there can be considerable variability. Rubbing the skin to dilate blood vessels in the immediate area increases the rate of absorption. Injection of a drug in a nonaqueous solution (such as peanut oil) or implantation of a drug pellet or delivery device further slows the rate of absorption. Subcutaneous implantation of drug-containing pellets is most often used to administer hormones. Implanon and Nexplanon are two contraceptive implants now available in the United States. The hormones are contained in a single small rod about 40 mm (1.5 inches) long that is implanted through a small incision just under the skin of the upper arm. A woman is protected from pregnancy for a 3-year period unless the device is removed. Recent technological advances allow drug solutions to be injected in a liquid form, which, upon contact with subcutaneous tissue fluid, forms a biodegradable solid or gel that slowly releases active drug over a period of up to 1 month. This technology has been used to administer buprenorphine, which acts as a partial agonist or antagonist at opioid receptors. This mechanism of action is thought to help individuals overcome opioid use disorder by reducing drug withdrawal and promoting treatment compliance due to the long duration of effect (see Ling et al., 2019; Rosenthal, 2019, for detailed reviews of the effectiveness of these novel formulations). Also, refer to Chapter 11 for information about the endogenous opioid system and drugs that act upon it.

Inhalation of drugs, such as those used to treat asthma attacks, allows drugs to be absorbed into the blood by passing through the lungs. Absorption is very rapid because the area of the pulmonary absorbing surfaces is large and rich with capillaries (see Figure 1.2). The effect on the brain is very rapid because blood from the capillaries of the lungs travels only a short distance back to the heart before it is pumped quickly to the brain via the carotid artery, which carries oxygenated blood to the head and neck. The psychoactive effects of inhaled substances can occur within a matter of seconds.

Inhalation is the method preferred for self-administration in cases when oral absorption is too slow and much of the active drug would be destroyed in the GI tract before it reached the brain. Nicotine released from the tobacco of a cigarette by heat into the smoke produces a very rapid rise in blood level and rapid central nervous system (CNS) effects, which peak in a matter of minutes. Tetrahydrocannabinol (THC), an active ingredient of marijuana, and crack cocaine are also rapidly absorbed after smoking. In addition to the inherent dangers of the drugs themselves, disadvantages of inhalation include irritation of the nasal passages and damage to the lungs caused by small particles that may be included in the inhaled material.

Topical application of drugs to mucous membranes, such as the conjunctiva of the eye, the oral cavity, nasopharynx, vagina, colon, and urethra, generally provides local drug effects. Because topically applied drugs are typically intended to act locally, this method of drug administration is generally not considered a systemic route of administration. However, some topically administered drugs can nevertheless be readily absorbed into the general circulation, leading to widespread effects. A related delivery method is **sublingual administration**, which involves placing the drug under the tongue, where it contacts the mucous membrane and is absorbed rapidly into a rich capillary network. Sublingual administration has several advantages over oral administration, because the drug is not broken down by gastric acid or gastric enzymes. Further, its absorption is faster because it is absorbed directly into the blood and is not dependent on those factors that determine how quickly the stomach empties its contents into the small intestine. Additionally, since the drug is not absorbed from the GI tract, it avoids first-pass metabolism. **Intranasal administration** is of special interest because it causes local effects such as relieving nasal congestion and treating allergies, but it can also have systemic effects, in which case the drug

moves very rapidly across a single epithelial cell layer into the bloodstream, avoiding first-pass liver metabolism and producing higher bioavailability than if given orally. The approach is noninvasive, painless, and easy to use, and hence it enhances compliance. Even more important is the fact that intranasal administration allows the blood–brain barrier to be bypassed, perhaps by achieving direct access to the fluid that surrounds the brain (**cerebrospinal fluid** [**CSF**]) and moving from there to extracellular fluid found in the intercellular spaces between neurons. (For a discussion of the potential mechanisms by which intranasal administration can bypass the blood–brain barrier, see Crowe et al., 2018.) A large number of drugs, hormones, steroids, proteins, peptides, and other large molecules are available in nasal spray preparations for intranasal delivery, although not all drugs can be atomized. Hence, neuropeptides such as the hormone oxytocin can be administered by intranasal sprays to achieve significant concentrations in the brain. **WEB BOX 1.2** describes a study that evaluated the effects of intranasal oxytocin administration on social behavior in autistic adults.

Intranasal absorption can also be achieved without dissolving the drug. Direct application of finely powdered cocaine to the nasal mucosa by sniffing leads to rapid absorption, which produces profound effects on the CNS that peak in about 15 to 30 minutes. One side effect of "snorting" cocaine is the formation of perforations in the nasal septum, the cartilage that separates the two nostrils. This damage occurs because cocaine is a potent vasoconstrictor. Reducing blood flow deprives the underlying cartilage of oxygen, leading to necrosis. Additionally, contaminants in the cocaine act as chemical irritants, causing tissue inflammation. Cocaine addicts whose nasal mucosa has been damaged by chronic cocaine "snorting" may resort to application of the drug to the rectum, vagina, or penis.

Although the skin provides an effective barrier to the diffusion of water-soluble drugs, certain lipid-soluble substances (i.e., those that dissolve in fat) are capable of penetrating slowly. Accidental absorption of industrial and agricultural chemicals such as tetraethyl lead, organophosphate insecticides, and carbon tetrachloride through the skin produces toxic effects on the nervous system and on other organ systems. **Transdermal** (i.e., through the skin) drug administration with skin patches provides controlled and sustained delivery of drug at a preprogrammed rate. The method is convenient because the individual does not have to remember to take a pill, and it is painless without the need for injection. It also provides the advantage of avoiding the first-pass effect. In cases of mass vaccination campaigns, transdermal delivery is much quicker than other methods, and it reduces the dangers of accidental needle sticks of health care workers and unsafe disposal of used needles. Conventional patches consist of a polymer matrix embedded with the drug in high concentration. Transdermal delivery is now a common way to prevent motion sickness with scopolamine, reduce cigarette craving with nicotine, relieve angina pectoris with nitroglycerin, and provide hormones after menopause or for contraceptive purposes. The major disadvantage of transdermal delivery is that because skin is designed to prevent materials from entering the body, a limited number of drugs are able to penetrate. However, techniques are continuing to be developed to increase skin permeability through a variety of methods. For instance, handheld ultrasound devices that send low-intensity sound energy waves through surrounding fluid in the tissue temporarily increase the size of the pores in the skin, allowing absorption of large molecules from a skin patch. Other "active" patch systems that help to move large molecules through the skin use iontophoresis, which involves applying a small electrical current with tiny batteries to the reservoir or the patch. The electrical charge repels drug molecules with a similar charge and forces them through the skin at a predetermined rate. If the amount and duration of current are changed, drug delivery can be restricted to the skin for local effects or can be forced more deeply into the blood. This process is also capable of pulling molecules out through the skin for monitoring. Such monitoring might be used by diabetic individuals to more frequently and painlessly evaluate levels of blood glucose. An additional approach uses mechanical disruption of the skin. Small arrays of microneedles about 1 μm in diameter and 100 μm long and coated with drug or vaccine are placed on the skin. The needles penetrate the superficial layer of the skin—the stratum corneum—where the drug is delivered without stimulating underlying pain receptors. This method provides the opportunity for painless vaccinations and drug injections that can be self-administered. These and other developing techniques have been described by Langer (2003), Banga (2009), and Waghule and colleagues (2019).

Special injection methods must be used for some drugs that act on nerve cells, because a cellular barrier, the blood–brain barrier (discussed later in the chapter), prevents or slows passage of these drugs from the blood into neural tissue. To directly bypass the blood–brain barrier, **central** routes of administration may be used. For example, **intrathecal** injection is used when spinal anesthetics are administered directly into the CSF in the subarachnoid space surrounding the spinal cord, whereas **epidural** infusion, in which a catheter is implanted in the epidural space just outside of the dura mater, is commonly used during childbirth, bypassing the blood–brain barrier (**FIGURE 1.3**). In animal experiments, a microsyringe or a cannula enables precise drug infusion into discrete areas of brain tissue (**intracranial**) or into

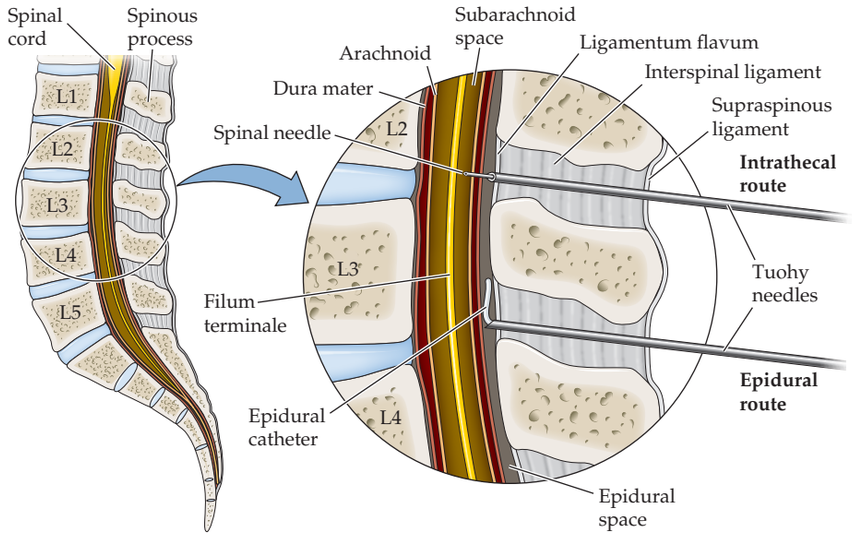

FIGURE 1.3 **Anatomical diagram of intrathecal and epidural routes of administration** (Left) Cross-section of the lumbar spine, illustrating the typical spinal level selected for intrathecal and epidural routes of administration. (Right) The intrathecal route of administration requires that the tip of the infusion catheter penetrate the dura mater and arachnoid membranes, allowing for drug to be infused directly into the subarachnoid space. In contrast, the epidural route uses a flexible catheter that targets the space outside of the dura mater (epidural space). (After F. Cox [Ed.]. 2009. *Perioperative Pain Management*. Wiley-Blackwell: Oxford.)

the CSF-filled chambers, the ventricles (**intracerebroventricular**). In this way, experimenters can study the electrophysiological, biochemical, or behavioral effects of drugs on particular nerve cell groups. This method is described in Chapter 4. Animal research has evolved into potentially important treatment methods for human conditions such as cerebral meningitis (inflammation of one of the protective membranes covering the brain). An **infusion pump** implanted under the skin of the scalp can be programmed to deliver a constant dose of antibiotic into the cerebral ventricles; this device permits treatment of brain infection and is useful because antibiotics are normally prevented from passing the blood–brain barrier. These infusion pumps have important uses in delivering drugs systemically as well. With appropriate software, it is possible to provide pulsed administration of an agent that mimics the normal biological rhythm, for example, of hormones. An exciting development has been the addition of feedback regulation of these pumps, which includes a sensor element that monitors a substance such as blood glucose in a diabetic individual and responds with an appropriate infusion of insulin delivered from an implantable pump that acts much like an artificial pancreas. The downside to these pumps is the risk of infection and frequent clogging, which reduces their usefulness in maintaining stable drug concentrations over prolonged periods.

Many disorders of the CNS are characterized by abnormal changes in gene activity, which alter the manufacture of an essential protein such as an enzyme or a receptor. **Gene therapy** refers to the application of deoxyribonucleic acid (DNA), which encodes a specific protein, to a particular target site. DNA can be used to increase or block expression of the gene product to correct the clinical condition. One significant difficulty in the application of gene therapy involves creating the appropriate gene delivery system. Such a delivery system, which is called a *vector*, is needed to carry the gene into the nuclei of target cells to alter protein synthesis. Administering gene therapy is clearly more challenging when disorders of the CNS, rather than disorders of any other part of the body, are treated. Vectors are usually injected directly into the brain region targeted for modification. **Viral vectors** are frequently considered for this delivery system because of the special ability of viruses to bind to and enter cells and their nuclei, where they insert themselves into the chromosomes to alter DNA. Because viruses vary in terms of binding, cell entry proteins, and other properties, a variety of viruses are being evaluated.

Lim and colleagues (2010) provide a review of viral vector delivery as an approach to treating diseases of the CNS. Human trials have been increasing in number, but much research remains to be done before the safety and usefulness of gene therapy are fully demonstrated. Concerns expressed by researchers include the following: that an immune response may be initiated by the introduction of foreign material, that the viral vector may recover its ability to cause disease once it is placed in the human cell, and that inserting the vector in the wrong place may induce tumor growth. Nevertheless, many animal studies are highly encouraging, and gene therapy is believed to have enormous potential for the treatment of debilitating disorders of the nervous system such as stroke-induced damage, spinal cord injury, chronic pain conditions, and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease.

IMPACT ON BIOAVAILABILITY Because the route of administration significantly alters the rate of absorption, blood levels of the same dose of a drug

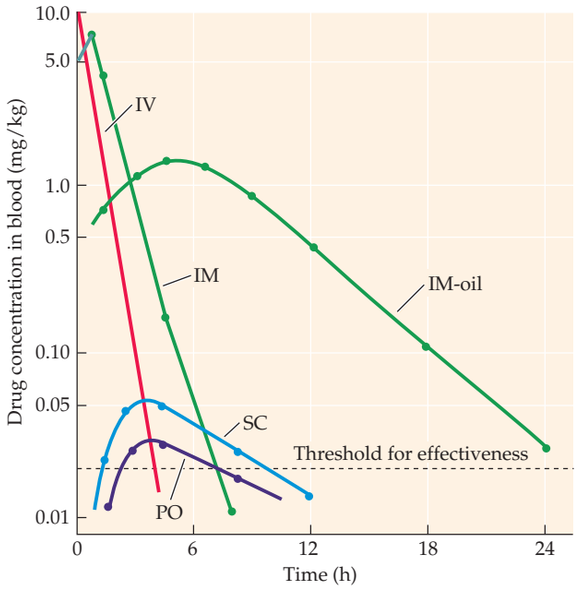

FIGURE 1.4 The time course of drug blood level depends on route of administration The blood level of the same amount of drug administered by different procedures to the same individual varies significantly. Intravenous (IV) administration produces an instantaneous peak when the drug is placed in the blood, followed by a rapid decline. Intramuscular (IM) administration produces rapid absorption and rapid decline, although IM administration in oil (IM-oil) shows slower absorption and gradual decline. Slow absorption after subcutaneous (SC) administration means that some of the drug is metabolized before absorption is complete. For this reason, no sharp peak occurs, and overall blood levels are lower. Oral (PO) administration produces the lowest blood levels and a relatively short time over threshold for effectiveness in this instance. (After R. R. Levine. 1973. *Pharmacology: Drug Actions and Reactions*. Little, Brown, and Co.: Boston; D. F. Marsh. 1951. *Outlines of Fundamental Pharmacology*. Charles C. Thomas: Springfield, IL.)

administered by different routes vary significantly. **FIGURE 1.4** compares drug concentrations in blood over time for various routes of administration. Keep in mind that the peak level for each method reflects not only differences in absorption rate, but also the fact that slow absorption provides the opportunity for liver metabolism to act on some of the drug molecules before absorption is complete. Advantages and disadvantages of selected methods of administration are summarized in **TABLE 1.1.**

Multiple factors modify drug absorption

Once the drug has been administered, it is absorbed from the site of administration into the blood to be circulated throughout the body and ultimately to the brain, which is the primary target site for **psychoactive drugs** (i.e., those drugs that have an effect on thinking, mood, and behavior). We have already shown that the rate of absorption is dependent on several factors. Clearly, the route of administration alters absorption because it determines the area of the absorbing surface, the number of cell layers between the site of administration and the blood, the amount of drug destroyed by metabolism or digestive processes, and the extent of binding to food or inert complexes. Absorption is also dependent on drug concentration, which is determined

TABLE 1.1 Advantages and Disadvantages of Selected Routes of Drug Administration

Route of administration	Advantages	Disadvantages
Oral (PO)	Safe; self-administered; economical; no needle-related complications	Slow and highly variable absorption; subject to first-pass metabolism; less-predictable blood levels
Intravenous (IV)	Most rapid; most accurate blood concentration	Overdose danger; cannot be readily reversed; requires sterile needles and medical technique
Intramuscular (IM)	Slow and even absorption	Localized irritation at site of injection; needs sterile equipment
Subcutaneous (SC)	Slow and prolonged absorption	Variable absorption depending on blood flow
Inhalation	Large absorption surface; very rapid onset; no injection equipment needed	Irritation of nasal passages; inhaled small particles may damage lungs
Topical	Localized action and effects; easy to self-administer	May be absorbed into general circulation
Transdermal	Controlled and prolonged absorption	Local irritation; useful only for lipid-soluble drugs
Epidural	Bypasses blood–brain barrier; very rapid effect on CNS	Not reversible; needs trained anesthesiologist; possible nerve damage
Intranasal	Ease of use; local or systemic effects; very rapid; no first-pass metabolism; bypasses blood–brain barrier	Not all drugs can be atomized; potential irritation of nasal mucosa

in part by individual differences in age, sex, and body size. Finally, absorption is dependent on the solubility and ionization of the drug.

TRANSPORT ACROSS MEMBRANES Perhaps the single most important factor in determining plasma drug levels is the rate of passage of the drug through the various cell layers (and their respective membranes) between the site of administration and the blood. To understand this process, we need to look more carefully at cell membranes.

Cell membranes are made up primarily of complex lipid (fat) molecules called **phospholipids**, which have a negatively charged phosphate region (the head) at one end and two uncharged lipid tails (**FIGURE 1.5A**). These molecules are arranged in a bilayer, with their phosphate ends forming two almost continuous sheets filled with fatty material (**FIGURE 1.5B**). This configuration occurs because the polar heads are attracted to the polar water molecules. Hence, the charged heads are in contact with both the aqueous intracellular fluid and the aqueous extracellular fluid. Proteins that are found inserted into the phospholipid bilayer have functions that will be described later (see Chapter 3). The molecular characteristics of the cell membrane prevent most molecules from passing through unless they are soluble in fat.

LIPID-SOLUBLE DRUGS Drugs with high lipid solubility move through cell membranes by **passive diffusion**, leaving the water in the blood or stomach juices and entering the lipid layers of membranes. Movement across the membranes is always in a direction from higher to lower concentration. The larger the concentration difference on each side of the membrane (called the **concentration gradient**), the more rapid is the diffusion. Lipid solubility increases the absorption of drug into the blood and determines how readily a drug will pass the lipid barriers to enter the brain. For example, the narcotic drug heroin is a simple modification of the parent compound morphine. Heroin, or diacetylmorphine, is more soluble in lipid than is morphine, and it penetrates into brain tissue more readily, thus having a quicker onset of action and more potent reinforcing properties. This occurs despite the fact that before the psychotropic drug effects occur, the heroin must be converted to morphine by esterase enzymes in the brain. That property makes heroin a prodrug—that is, one that is dependent on metabolism to convert an inactive drug to an active one, a process called **bioactivation**. This strategy is one used by pharmaceutical companies that develop prodrugs that cross the blood–brain barrier (see the section Drug Distribution Is Limited by Selective Barriers) if the active drug cannot penetrate easily.

IONIZED DRUGS Most drugs are not readily lipid soluble, because they are weak acids or weak bases that can become ionized when dissolved in water. Just as common table salt (NaCl) produces positively charged ions (Na^+) and negatively charged ions (Cl^-) when dissolved in water, many drugs form two charged (ionized) particles when placed in water. Although NaCl is a strong electrolyte, which causes it to almost entirely dissociate in water, most drugs are only partially ionized when dissolved in water. The extent of **ionization**

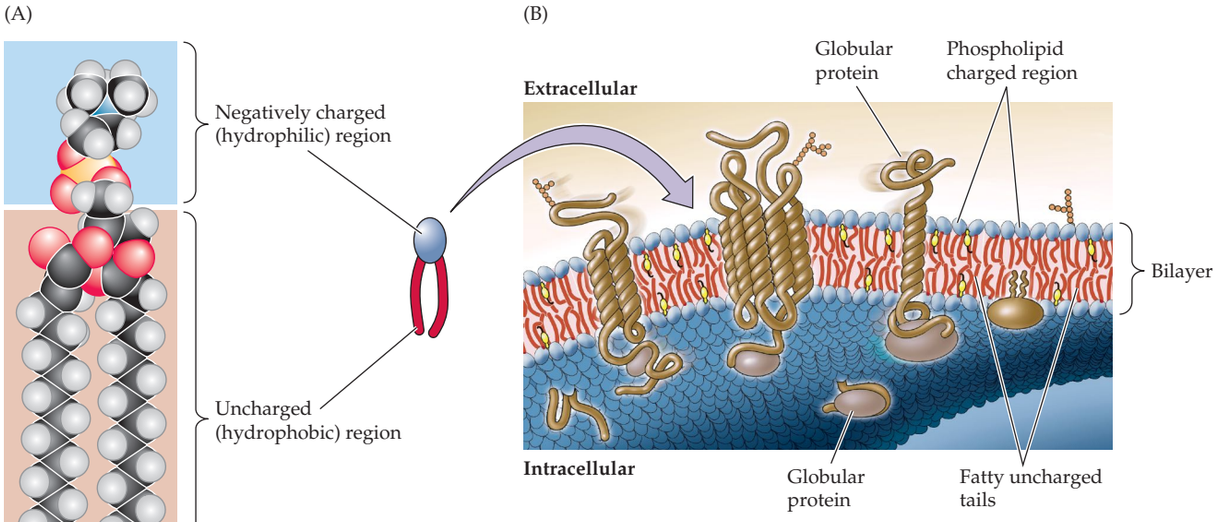

FIGURE 1.5 **Cell membranes** (A) Example of a phospholipid molecule with a negatively charged group (PO_4^-) at one end (hydrophilic) and two fatty uncharged tails (hydrophobic). (B) The arrangement of individual phospholipid molecules forms a bilayer, with negatively charged heads attracted to the water molecules of both intracellular and extracellular fluids. The fatty tails of the molecules are tucked within the two charged layers and have no contact with aqueous fluid. Embedded in the bilayer are protein molecules that serve as receptors or channels.

TABLE 1.2 pH of Body Fluids

Fluid	pH
Stomach	1.35–3.5
Blood	7.35–7.4
Kidney urine	4.6–8.0
Cerebrospinal fluid (CSF)	7.3

Source: After G. K. Schwalfenberg. 2012. *J Environ Public Health* 2012: 727630.

depends on two factors: the relative acidity/alkalinity (pH) of the solution, and an intrinsic property of the molecule (pK_a).

Acidity or alkalinity is expressed as pH, which is described on a scale of 1 to 14, with 7 being neutral. Acidic solutions have a lower pH, and alkaline (basic) solutions have a pH greater than 7.0. Drugs are dissolved in body fluids that differ in pH (**TABLE 1.2**), and these differences play a role in drug ionization and movement from one body fluid compartment to another, for example from the stomach to the bloodstream, or from the bloodstream into the kidney urine.

The second factor determining ionization is a characteristic of the drug molecule. The pK_a of a drug represents the pH of the aqueous solution in which that drug would be 50% ionized and 50% non-ionized. In general, drugs that are weak acids ionize more readily in an alkaline environment and become less ionized in an acidic environment. The reverse is true of drugs that are weak bases. If we put the weak acid aspirin (acetylsalicylic acid) into stomach acid, it will remain primarily in a non-ionized form (**FIGURE 1.6**). The lack of electrical charge makes the drug more lipid soluble and hence readily absorbed from the stomach to the blood. In the intestine, where the pH is around 5.0 to 6.0, ionization increases and absorption through that membrane is reduced compared with that of the stomach.

This raises the question of why aspirin molecules do not move from the stomach to the blood and back to the stomach again. In our example, aspirin in the acidic gastric fluid is primarily in non-ionized form and thus passes through the stomach wall into the blood. In blood (pH 7.4), however, aspirin becomes more ionized; it is said to be "trapped" within the blood and does not return to the stomach. Meanwhile, the circulation moves the aspirin molecules away from their concentrated site at the stomach to maintain a concentration gradient that favors drug absorption. Hence, although passive diffusion would normally cease when drug concentration approached a 50:50 equilibrium, the combination of ion trapping and blood circulation of the drug away from the absorbing surface means that absorption from oral administration can be quite high. Keep in mind that although the acidic stomach favors absorption of weak acids, much of the aspirin

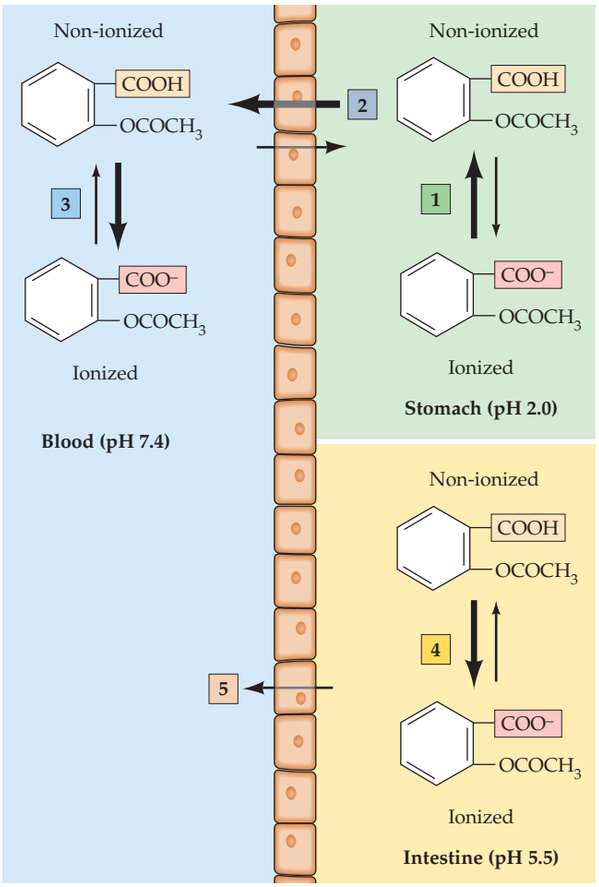

FIGURE 1.6 Effect of ionization on drug absorption On the right side of the cell barrier in stomach acid (pH 2.0), aspirin molecules tend to remain in the non-ionized form (1), which promotes the passage of the drug through the cell walls (2) to the blood. Once the intact aspirin molecules reach the blood (pH 7.4), they ionize (3) and are "trapped" in the blood to be circulated throughout the body. In the lower portion of the figure, when the aspirin has reached the intestine, it tends to dissociate to a greater extent (4) in the more basic pH. Its more ionized form reduces passage (5) through the cells to the blood, so absorption from the intestine is slower than from the stomach.

is absorbed in the small intestine because absorption is also determined by the length of time the drug is in contact with the absorptive membrane.

Drugs that are highly charged in both acidic and basic environments are very poorly absorbed from the GI tract and cannot be administered orally. This explains why South American hunters readily eat the flesh of game killed with curare-poisoned arrows. Curare is highly ionized in both the acidic stomach and the alkaline intestine, so the drug does not leave the digestive system to enter their blood.

OTHER FACTORS Factors other than ionization have a significant influence on absorption as well. For instance, the much larger surface area of the small

intestine and the slower movement of material through the intestine, as compared with the stomach, provide a much greater opportunity for absorption of all drugs. Therefore, the rate at which the stomach empties into the intestine very often is the significant rate-limiting factor. For this reason, medication is often prescribed to be taken before meals and with sufficient fluid to move the drug through the stomach and into the intestine.

Since drug absorption is closely related to the concentration of the drug in body fluids (e.g., stomach), it should certainly be no surprise to you that the drug dosage required to achieve a desired effect is directly related to the size of the individual. In general, the larger the individual, the more diluted the drug will be in the larger fluid volume, and less drug will reach target sites within a given unit of time. The average dose of a drug is typically based on the response of individuals between the ages of 18 and 65 who weigh 150 pounds. However, for people who are very lean or obese, the average dose may be inappropriate because of variations in the ratio of fat to water in the body. For these individuals, body surface area, which reflects both size and weight, may serve as a better basis for determining drug dose. The sex of the individual also plays a part in determining plasma drug level: in women, adipose tissue, relative to water, represents a larger proportion of the total body weight. Overall, the total fluid volume, which contains the drug, is relatively smaller in women than in men, producing a higher drug concentration at the target site in women. It should be obvious also that in the smaller fluid volume of a child, a standard dose of a drug will be more concentrated and therefore will produce a greater drug effect.

Drug distribution is limited by selective barriers

Regardless of the route of administration, once the drug has entered the blood, it is carried throughout the body within 1 or 2 minutes and can have an action at any number of receptor sites. In general, those parts of the body in which blood flow is greatest will have the highest concentration of drug. Since blood capillaries have numerous pores, most drugs can move from blood and enter body tissues regardless of lipid solubility, unless they are bound to protein (see the discussion on depot binding later in this chapter). Quite rapidly, high concentrations of drugs will be found in the heart, brain, kidneys, and liver. Other tissues with less vasculature will more slowly continue to absorb the drug from the plasma, causing plasma levels to fall gradually. As plasma levels fall, the concentration of drug in the highly vascularized organs will be greater than that in the blood, so the drug will move from those organs back into the plasma to maintain equilibrium. Hence, those organs will have an initial high concentration of drug, and then **drug redistribution** will reduce drug concentration there. Ultimately drug concentration will be in equilibrium in all tissues. Drug redistribution may be responsible for terminating the action of a drug, as in the case of the rapid-acting CNS depressant thiopental. Thiopental, a barbiturate used for intravenous anesthesia, is highly lipid soluble; therefore, rapid onset of sedation is caused by entry of the drug into the brain. Deep sedation does not last very long, because the blood level falls rapidly as a result of redistribution of the drug to other tissues, causing thiopental to move from the brain to the blood to maintain equilibrium. High levels of thiopental can be found in the brain 30 seconds after IV infusion. However, within 5 minutes, brain levels of the drug drop to threshold anesthetic concentrations. In this way, thiopental induces sleep almost instantaneously but is effective for only about 5 minutes, followed by rapid recovery.

Because the brain receives about 20% of the blood that leaves the heart, lipid-soluble drugs are readily distributed to brain tissue. However, the blood–brain barrier limits the movement of ionized molecules from the blood to the brain.

BLOOD–BRAIN BARRIER Blood plasma is supplied by a dense network of blood vessels that permeate the entire brain. This system supplies brain cells with oxygen, glucose, and amino acids, and it carries away carbon dioxide and other waste products. Despite the vital role that blood circulation plays in cerebral function, many substances found in blood fluctuate significantly and would have disruptive effects on brain cell activity if materials were transferred freely between blood and brain (and the brain's associated CSF).

CSF is a clear, colorless liquid that fills the subarachnoid space that surrounds the entire bulk of the brain and spinal cord and also fills the hollow spaces (ventricles) and their interconnecting channels (aqueducts), as well as the centrally located cavity that runs longitudinally through the length of the spinal cord (central canal) (**FIGURE 1.7A**). CSF is manufactured by cells of the choroid plexus, which line the cerebral ventricles. In contrast to the wide fluctuations that occur in the blood plasma, the contents of the CSF remain quite stable. Many substances that diffuse out of the blood and affect other organs in the body do not seem to enter the CSF, nor do they affect brain tissue. This separation between brain capillaries and the brain/CSF constitutes what we call the blood–brain barrier. **FIGURE 1.7B** shows an enlargement of the relationship between the cerebral blood vessels and the CSF.

The principal component of the blood–brain barrier is the distinct morphology of brain capillaries. **FIGURE 1.8** shows a comparison between typical capillaries found throughout the body (Figure 1.8A) and capillaries that serve the CNS (Figure 1.8B). Because the job of blood vessels is to deliver nutrients to cells while removing waste, the walls of typical capillaries are made up of endothelial cells that have both small gaps (**intercellular clefts**)

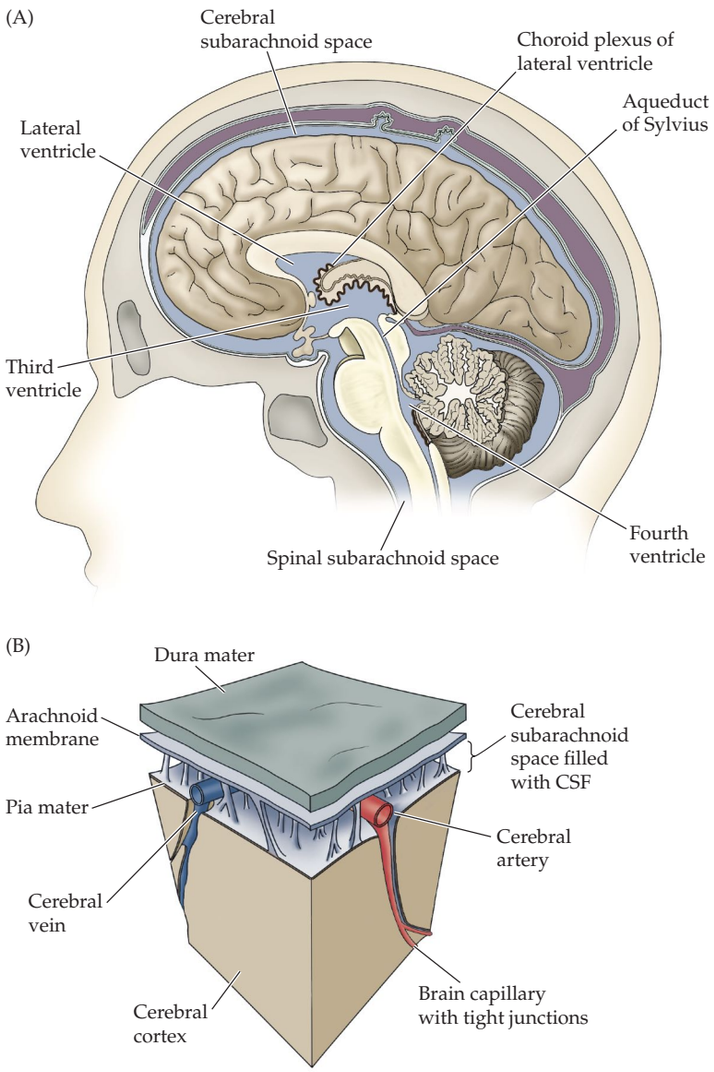

FIGURE 1.7 **Distribution of cerebrospinal fluid** (A) Cerebrospinal fluid (CSF; blue) is manufactured by the choroid plexus within the cerebral ventricles. In addition to filling the ventricles and their connecting aqueducts, CSF fills the space between the arachnoid membrane and the pia mater (subarachnoid space) to cushion the brain against trauma. (B) The enlarged diagram shows detail of CSF-filled subarachnoid space and its relationship to cerebral blood vessels. Note how the blood vessels penetrate the brain tissue.

and larger openings (**fenestrations**) through which molecules can pass. In addition, general capillaries have **pinocytotic vesicles** that envelop and transport larger molecules through the capillary wall. In contrast, in brain capillaries, the intercellular clefts are closed because adjoining edges of the endothelial cells are fused, forming **tight junctions**. Also, fenestrations are absent and pinocytotic vesicles are rare. Although lipid-soluble materials can pass through the walls of the blood vessels, most materials are moved from the blood of brain capillaries by special transporters. Surrounding brain capillaries are numerous glial feet—extensions of the glial cells called **astrocytes** or **astroglia**. It is becoming apparent that these astrocytic glial feet contribute to both postnatal formation and maintenance of the blood–brain barrier throughout adulthood. It has been shown that blood–brain barrier characteristics depend on the CNS environment, because if the endothelial cells are removed and cultured without astroglia, they lose their barrier function. Conversely, blood–brain barrier characteristics can be induced in non-CNS endothelial cells that are cultured with astrocytes (see Alvarez et al., 2013). By filling in the extracellular space around capillaries and releasing secretion factors, these astroglia apparently help maintain the endothelial tight junctions. Also, it is likely that the close interface of astrocytes with both nerve cells and brain capillaries provides the astrocytes with a unique opportunity to coordinate the delivery of oxygen and glucose in the blood with the energy required by activated neurons. There is more discussion of the many functions of astrocytes in Chapter 2.

Before we go on, we should emphasize that the blood–brain barrier is selectively permeable, not impermeable. Although the barrier does reduce diffusion of water-soluble (i.e., ionized) molecules, it does not impede lipid-soluble molecules.

Finally, the blood–brain barrier is not complete. Several brain areas are not isolated from materials in the blood, and a limited blood–brain barrier exists in other regions of the brain wherever a functional interaction (e.g., blood monitoring) is required between blood and neural tissue. For example, the area postrema, or chemical trigger zone, is a cluster of cells in the brainstem that responds to toxins in the blood and induces vomiting.

The limited permeability of the blood–brain barrier is important in psychopharmacology because we need to know which drugs remain non-ionized at plasma pH and readily enter the CNS, and which drugs only circulate throughout the rest of the body. Minor differences in drug molecules are responsible for the relative selectivity of drug action. For example, physostigmine readily crosses the blood–brain barrier and is useful for treating the intoxication caused by some agricultural pesticides. It does so by increasing the availability of the neurotransmitter acetylcholine.

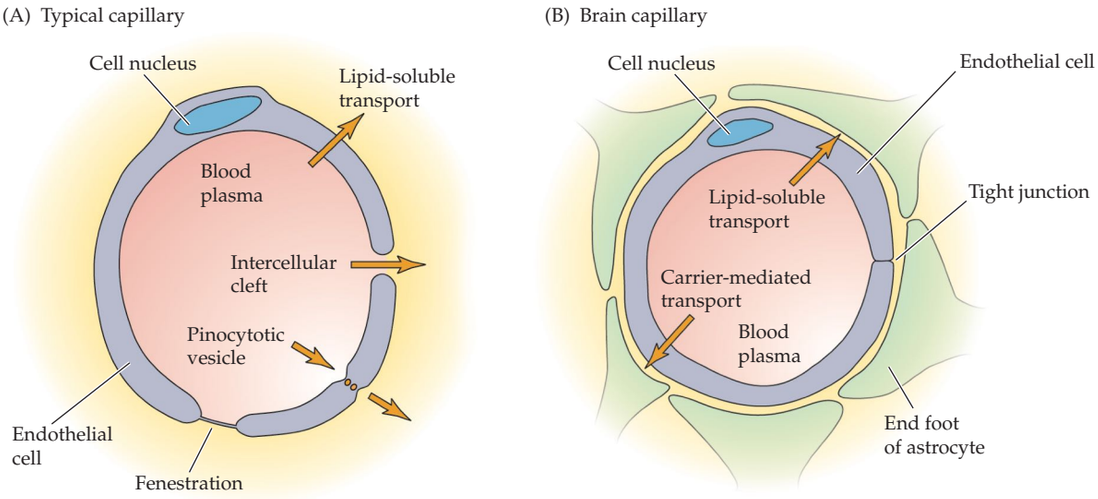

FIGURE 1.8 Cross-section of typical capillaries and brain capillaries (A) Capillaries found throughout the body have characteristics that encourage movement of materials between the blood and surrounding cells. (B) Brain capillaries minimize movement of water-soluble molecules through the blood vessel wall because there are essentially no large or small clefts or pinocytotic sites. (After W. H. Oldendorf. 1977. *Exp Eye Res* 25: 177–190. © 1977. Reprinted with permission from Elsevier.)

In contrast, the structurally related but highly ionized drug neostigmine is excluded from the brain and increases acetylcholine only peripherally. Its restriction by the blood–brain barrier means that neostigmine can be used to treat the muscle disease myasthenia gravis without significant CNS side effects, but it would not be effective in treating pesticide-induced intoxication. As mentioned earlier in this section, because many drugs that are ionized do not pass through the blood–brain barrier, direct delivery of the drug into brain tissue by intracranial injection may be necessary, although at least some drugs can be atomized and delivered intranasally to bypass the blood–brain barrier. A second approach is to develop a prodrug that is lipid soluble and becomes bioactivated by brain enzymes.

PLACENTAL BARRIER A second barrier, unique to women, is found between the blood circulation of a pregnant mother and that of her fetus. The placenta, which connects the fetus with the mother's uterine wall, is the means by which nutrients obtained from the digestion of food, O_2, CO_2, fetal waste products, and drugs are exchanged. As is true for other cell membranes, lipid-soluble substances diffuse easily, and water-soluble substances pass less easily. The potential for transfer of drugs from mother to fetus has very important implications for the health and well-being of the developing child. Potentially damaging effects on the fetus can be divided into two categories: acute toxicity and teratogenic effects.

The fetus may experience acute toxicity in utero after exposure to the disproportionately high drug blood level of its mother. In addition, after birth, any drug remaining in the newborn's circulation is likely to have a dramatic and prolonged action because of slow and incomplete metabolism. It is well known that opiates such as heroin readily reach the fetal circulation and that newborn infants of heroin- or methadone-addicted mothers experience many of the signs of opiate withdrawal. Certain tranquilizers, gaseous anesthetics, alcohol, many barbiturates, and cocaine all readily pass into the fetal circulation to cause acute toxicity. In addition, alcohol, cocaine, and the carbon monoxide in cigarette smoke all deprive the fetus of oxygen. Such drugs pose special problems because they are readily accessible and are widely used.

Teratogens are agents that induce developmental abnormalities in the fetus. The effects of teratogens such as drugs (both therapeutic and illicit), exposure to X-rays, and some maternal infections (e.g., German measles) are dependent on the timing of exposure. The fetus is most susceptible to damaging effects during the first trimester of pregnancy, because it is during this period that many of the fetal organ systems are formed. Each organ system is maximally sensitive to damaging effects during its time of cell differentiation (**TABLE 1.3**). Many drugs can have damaging effects on the fetus despite minimal adverse effects in the mother. For example, the vitamin A–related substance isotretinoin, which is a popular prescription acne medication (Accutane), produces serious birth defects and must be avoided by sexually active young women. Experience has taught us that evaluation of drug safety must consider potential fetal effects, as well as effects on adults. Furthermore, because teratogenic effects are most severe during the time before pregnancy is typically recognized, the use of any drug known to be teratogenic in animals should be avoided by women of childbearing age.

TABLE 1.3 Critical Periods of Teratogenic Sensitivity for Several Organ Systems in the Human Fetus

Organ system	Weeks after fertilization
Brain	3–16
Eye	4–8
Genitalia	7–9
Heart	3–6
Limbs	4–6

Depot binding alters the magnitude and duration of drug action

We already know that after a drug has been absorbed into the blood from its site of administration, it circulates throughout the body. Thus, high concentrations of drug may be found in all organs that are well supplied with blood until the drug gradually redistributes to all tissues in the body. Drug binding occurs at many inactive sites, where no measurable biological effect is initiated. Such sites, called **drug depots** or **silent receptors**, include several plasma proteins, with albumin being most important. Any drug molecules bound to these depots cannot reach active sites, nor can they be metabolized by the liver. However, the drug binding is reversible, so the drug remains bound only until the blood level drops, causing it to unbind gradually and circulate in the plasma.

The binding of a drug to inactive sites—called **depot binding**—has significant effects on the magnitude and duration of drug action. Some of these effects are summarized in **TABLE 1.4**. First, depot binding reduces the concentration of drug at its sites of action because only freely circulating (unbound) drug can pass across membranes. Onset of action of a drug that binds readily to depot sites may be delayed and its effects reduced because the number of drug molecules reaching the target tissue is dependent on its release from inactive sites. Individual differences in the amount of depot binding explain in part why some people are more sensitive than others to a particular drug.

Second, because binding to albumin, fat, and muscle is rather nonselective, many drugs with similar physiochemical characteristics compete with each other for these sites. Such competition may lead to a much-higher-than-expected free drug blood level of the displaced drug, producing a drug overdose. For example, the antiseizure drug phenytoin is highly protein bound, but aspirin can displace some of the phenytoin molecules from the binding sites because aspirin binds more readily. When phenytoin is displaced from plasma protein by aspirin, the elevated drug level may be responsible for unexpected side effects. Many psychoactive drugs, including the antidepressant fluoxetine (Prozac) and the tranquilizer diazepam (Valium), show extensive (more than 90% of the drug molecules) plasma protein binding and may contribute to drug interactions in some cases.

Third, bound drug molecules cannot be altered by liver enzymes, because the drug is not free to leave the blood to enter liver cells for metabolism. For this reason, depot binding frequently prolongs the time that the drug remains in the body. This phenomenon explains why some drugs, such as THC, which is stored in fat and is only slowly released, can be detected in urine for many days after a single dose. Such slow release means that an individual could test positive for urinary THC (one active ingredient in marijuana) without experiencing cognitive effects at that time. The prolonged presence of drugs in body fat and inert depots makes pre-employment and student drug testing possible.

Finally, as mentioned previously, redistribution of a drug from highly vascularized organs (e.g., brain) to tissues with less blood flow will reduce drug concentrations in those organs. The redistribution occurs more rapidly for highly lipid-soluble drugs that reach the

TABLE 1.4 Effects of Drug Depot Binding on Therapeutic Outcome

Depot-binding characteristics	Therapeutic outcome
Rapid binding to depots before reaching target tissue	Slower onset and reduced effects
Individual differences in amount of binding	Varying effects: High binding means less free drug, so some people seem to need higher doses. Low binding means more free drug, so these individuals seem more sensitive.
Competition among drugs for depot-binding sites	Higher-than-expected blood levels of the displaced drug, possibly causing greater side effects, even toxicity
Unmetabolized bound drug	Drug remaining in the body for prolonged action
Redistribution of drug to less vascularized tissues and inactive sites	Termination of drug action

brain very quickly but also redistribute readily because of the ease of movement through membranes. Those drugs have a rapid onset but short duration of action.

Biotransformation and elimination of drugs contribute to bioavailability

Drugs are eliminated from the body through the combined action of several mechanisms, including biotransformation (metabolism) of the drug and excretion of metabolites that have been formed. Drug clearance reduces blood levels and in large part determines the intensity and duration of drug effects. The easiest way to assess the rate of elimination consists of intravenously administering a drug to establish a peak plasma drug level, then collecting repeated blood samples. The decline in plasma drug concentration provides a direct measure of the clearance rate without complication by absorption kinetics.

DRUG CLEARANCE Drug clearance from the blood usually occurs exponentially and is referred to as **first-order kinetics**. Exponential elimination means that a constant *fraction* (50%) of free drug in the blood is removed during each time interval. The exponential function occurs because even at relatively high drug concentrations, surplus clearance sites are available, so the rate is concentration-dependent. Hence, when blood levels are high, clearance occurs more rapidly, and as blood levels drop, the rate of clearance is reduced. The amount of time required for removal of 50% of the drug in blood is called the **half-life**, or $t_{½}$. **FIGURE 1.9** provides an example of half-life determination for the stimulant dextroamphetamine (Dexedrine), a drug used to treat attention-deficit/hyperactivity disorder (ADHD). Although all drugs are essentially eliminated after six half-lives, many psychoactive drugs have half-lives of several days, so clearance may take weeks after even a single dose. A list of the half-lives of some common drugs is provided in **TABLE 1.5**. Keep in mind that clearance from the blood is also dependent on biotransformation rate as well as depot binding and storage in reservoirs such as fat.

The principal goal of any drug regimen is to maintain the plasma concentration of the drug at a constant desired level for a therapeutic period. The therapeutic window is the range of plasma drug levels that are high enough to be effective, but not so high that they cause toxic or otherwise intolerable side effects. For some drugs, such as stimulants used to treat ADHD, or hypnotic drugs used to promote sleep, the therapeutic period is only part of each day, so a single daily dose of a drug with a relatively short half-life would be required to avoid disruptive effects at other times of day. However, in many cases the target therapeutic concentration is achieved only after multiple administrations. For instance, as **FIGURE 1.10** shows, a predictable fluctuation in blood level occurs over

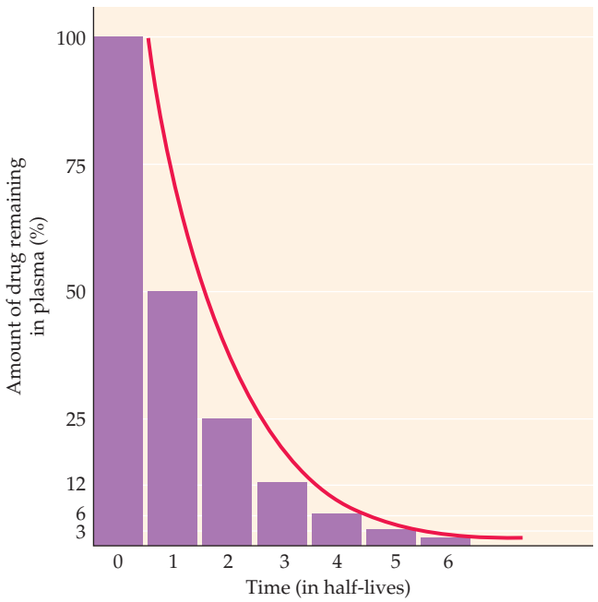

FIGURE 1.9 First-order kinetics of drug clearance Exponential elimination of drug from the blood occurs when clearance during a fixed time interval is always 50% of the drug remaining in blood. For example, the half-life of orally administered dextroamphetamine (Dexedrine) is approximately 10 hours. Therefore, 10 hours (one half-life) after the peak plasma concentration has been reached, the drug concentration is reduced to about 50% of its initial value. After 20 and 30 hours (i.e., two and three half-lives) have elapsed, the concentration is reduced to 25% and 12.5%, respectively. After six half-lives, the drug is essentially eliminated, with 1.6% remaining. The curve representing the rate of clearance is steeper early on, when the rate is more rapid, and becomes more shallow as the rate of clearance decreases.

time as a result of the dynamic balance between absorption and clearance. After oral administration at time A, the plasma level of a drug gradually increases to its peak (peak 1) followed by a decrease because of drug biotransformation, elimination, or storage at inactive sites. If first-order kinetics is assumed, after one half-life (time B), the plasma drug level has fallen to half its peak value. Half-life determines the time needed to reach the **steady state plasma level**, which is the desired blood concentration of drug achieved when the absorption/distribution phase is equal to the metabolism/excretion phase. For any given daily dose of a drug, the steady state plasma level is approached after a period of time equal to five half-lives (time C), at which point only 3.125% of the initial dose theoretically remains, minimally contributing to the total drug concentration achieved with subsequent doses. Hence, for a given dosing interval, the shorter the half-life of a drug, the more rapidly the therapeutic level of the drug will be achieved. Drugs with longer half-lives will take longer to reach consistent blood

TABLE 1.5 Half-Lives of Some Common Drugs

Drug	Half-life
Cocaine	0.7–1.5 hours[a]
Morphine	2–3.52 hours[b]
Nicotine	2 hours[c]
Methylphenidate	2–3 hours[d]
THC	20–30 hours[e]
Ibuprofen	1.8-2 hours[f]
Sertraline	22-36 hours[g]

Sources: Based on data in [a]J. L. Zimmerman. 2012 *Crit Care Clin* 28: 517–526; [b]C. E. Inturrisi. 2002. *Clin J of Pain* 18: S3; [c]N. L. Benowitz et al. 1982. *J Pharmacol Exp Ther* 221: 368–372; [d]H. C. Kimko et al. 1999. *Clin Pharmacokinet* 37: 457–470; [e]F. Grotenhermen. 2003. *Clin Pharmacokinet* 42: 327–360; [f]R. Bushra and N. Aslam 2010. *Oman Med J* 25: 55–1661; and [g]C. L. DeVane et al. 2002. *Clin Pharmacokinet* 41: 1247–1266.

levels. For example, if we needed the blood level of drug X with a half-life of 4 hours to be 1000 mg, we might administer 500 mg at the outset. After 4 hours, the blood level would have dropped to 250 mg, at which time we could administer another 500 mg, raising the blood level to 750 mg. Four hours later, another 500 mg could be added to the current blood level of 375 mg, bringing the new value to 875 mg, and so forth. The amount of drug would continue to rise until a maximum of 1000 mg was reached because more drug was given than was metabolized. However, as we reached the steady state level after approximately five half-lives, the amount administered would approximate the amount metabolized (500 mg).

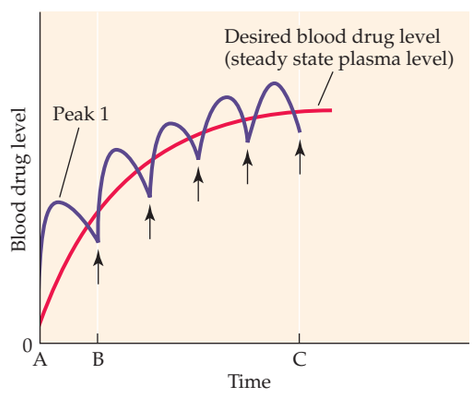

FIGURE 1.10 Achieving steady state plasma levels of drug The scalloped line shows the pattern of accumulation during repeated administration of a drug. The arrows represent the times of administration. The shape of the scallop is dependent on both the rate of absorption and the rate of elimination. The smooth line represents drug accumulation in the blood during continuous intravenous infusion of the same drug.

Although most drugs are cleared from the blood by first-order kinetics, under certain conditions some drugs are eliminated according to the zero-order model. **Zero-order kinetics** means that drug molecules are cleared at a constant rate regardless of drug concentration; this is graphically represented as a straight line (**FIGURE 1.11**). It happens when drug levels are high and routes of metabolism or elimination are saturated (i.e., more drug molecules are available than sites). A classic example of a drug that is eliminated by zero-order kinetics is high-dose ethyl alcohol. When two or more drinks of alcohol are consumed in a relatively short time, alcohol molecules saturate the enzyme-binding sites, and metabolism occurs at its maximum rate of approximately 10 to 15 ml/hour, or 1.0 ounce of 100-proof alcohol per hour regardless of concentration. This rate is determined by the number of enzyme molecules. Any alcohol consumption that occurs after saturation of the enzyme will raise blood levels dramatically and produce intoxication. Although zero-order biotransformation occurs at high levels of alcohol, the biotransformation rate shifts to first-order kinetics as blood levels are reduced (see Figure 1.11).

BIOTRANSFORMATION BY LIVER MICROSOMAL ENZYMES Most drugs are chemically altered by the body before they are excreted. These chemical changes

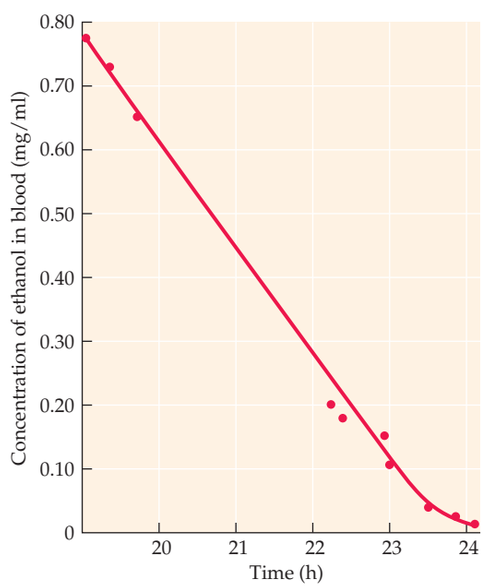

FIGURE 1.11 Zero-order rate of elimination The curve shows the decline of ethanol content in blood after intravenous administration of a large dose to laboratory animals. The *x*-axis represents the time beginning 19 hours after administration. Plotted data show the change from zero-order to first-order kinetics when low concentrations are reached between 23 and 24 hours after administration. (After E. K. Marshall, Jr. 1953. *J Pharmacol Exp Ther* 109: 431.)

are catalyzed by enzymes and can occur in many tissues and organs, including the stomach, intestine, blood plasma, kidney, and brain. However, the greatest number of chemical changes, which we call *drug metabolism* or biotransformation, occur in the liver.

There are two major types of biotransformation. Type I biotransformations are sometimes called phase I because these reactions often occur before a second metabolic step. Phase I changes involve *nonsynthetic* modification of the drug molecule by oxidation, reduction, or hydrolysis. Oxidation is by far the most common reaction; it usually produces a metabolite that is less lipid soluble and less active, but it may produce a metabolite with equal or even greater activity than the parent drug. Type II, or phase II, modifications are *synthetic* reactions that require the combination (called *conjugation*) of the drug with some small molecule such as glucuronide, sulfate, or methyl groups. Glucuronide conjugation is particularly important for inactivating psychoactive drugs. These metabolic products are less lipid soluble because they are highly ionized and are almost always biologically inactive. In summary, the two phases of drug biotransformation ultimately produce one or more inactive metabolites, which are water soluble, so they can be excreted more readily than the parent drug. Metabolites formed in the liver are returned to the circulation and are subsequently filtered out by the kidneys, or they may be excreted into bile and eliminated with the feces. Metabolites that are active return to the circulation and may have additional action on target tissues before they are further metabolized into inactive products. Obviously, drugs that are converted into active metabolites have a prolonged duration of action. **TABLE 1.6** shows several examples of the varied effects of phase I and phase II metabolism. The sedative drug phenobarbital is rapidly inactivated by phase I metabolism. In contrast, aspirin is converted at first to an active metabolite by phase I metabolism, but phase II action produces an inactive compound. Morphine does not undergo phase I metabolism but is inactivated by phase II reactions. Finally, diazepam (Valium), a long-lasting antianxiety drug, has several active metabolites before phase II inactivation. Further, as mentioned previously, some drugs are inactive until they are metabolized. For example, the inactive drug codeine is metabolized in the body to the active drug morphine, making codeine a prodrug.

The liver enzymes primarily responsible for metabolizing psychoactive drugs are located on the smooth endoplasmic reticulum, which is a network of tubules within the liver cell cytoplasm. These enzymes are often called **microsomal enzymes** because they exhibit particular characteristics on biochemical analysis. Microsomal enzymes lack strict specificity and can metabolize a wide variety of xenobiotics (i.e., chemicals that are foreign to the living organism), including toxins ingested with food, environmental pollutants, and carcinogens, as well as drugs. Among the most important liver microsomal enzymes is the **cytochrome P450** (**CYP450**) enzyme family. Members of this class of enzyme, which number more than 50, are responsible for oxidizing most psychoactive drugs, including antidepressants, morphine, and amphetamines. Although they are primarily found in the liver, cytochrome enzymes are also located in the intestine, kidney, lungs, and nasal passages, where they alter foreign molecules. Enzymes are classified into families and subfamilies by their amino acid sequences, as well as by the genes encoding them, and they are designated by a number—letter—number sequence such as 2D6. Among the cytochrome enzymes that are particularly important for psychotropic drug metabolism are CYP450 1A2, 3A4, 2D6, and several in the 2C subfamily.

FACTORS INFLUENCING DRUG METABOLISM The enzymes of the liver are of particular interest to psychopharmacologists because several factors significantly influence the rate of biotransformation. These factors alter the magnitude and duration of drug effects and are responsible for significant drug interactions. These drug interactions can either increase bioavailability, causing adverse effects, or reduce blood levels, which may reduce drug effectiveness. Additionally, variations in the rate of metabolism explain many of the individual differences seen in response to drugs. Factors that modify biotransformation capacity include (1) enzyme induction, (2) enzyme inhibition, (3) drug competition, and (4) individual differences in age, gender, and genetics.

TABLE 1.6 Varied Effects of Phase I and Phase II Metabolism

Active drug	Active metabolites and inactive metabolites[a]
Phenobarbital	—Phase I→ Hydroxy-phenobarbital
Aspirin	—Phase I→ **Salicylic acid** —Phase II→ Salicylic-glucuronide
Morphine	—Phase II→ Morphine-6-glucuronide
Diazepam	—Phase I→ **Desmethyldiazepam** —Phase II→ **Oxazepam** —Phase II→ Oxazepam-glucuronide

[a]Bold terms indicate active metabolites.

Many psychoactive drugs, when used repeatedly, cause an increase in a particular liver enzyme (called **enzyme induction**). Increased numbers of enzyme molecules not only cause the drugs to speed up their own rate of biotransformation two- to threefold but also can increase the rate of metabolism of all other drugs modified by the same enzyme. For example, repeated use of the antiseizure drug carbamazepine (Tegretol) increases the number of CYP450 3A4 enzyme molecules, leading to more rapid metabolism of carbamazepine and many other drugs, producing a lower blood level and a reduced biological effect. Among the drugs metabolized by the same enzyme are oral contraceptives. For this reason, if carbamazepine is prescribed to a woman who is taking oral contraceptives, she will need an increased hormone dose or an alternative means of birth control (Zajecka, 1993). When drug use is terminated, there is a gradual return to normal levels of metabolism.

Another common example is cigarette smoke, which increases CYP450 1A2 enzymes. People who are heavy smokers may need higher doses of drugs such as antidepressants and caffeine that are metabolized by the same enzyme. Such changes in drug metabolism and elimination explain in part why some drugs lose their effectiveness with repeated use, a phenomenon known as *tolerance* (see the discussion on tolerance later in the chapter); these changes also cause a reduced effect of other drugs that are metabolized by the same enzyme (cross-tolerance). Clearly, drug-taking history can have a major impact on the effectiveness of the drugs that an individual currently takes.

In contrast to drug-induced induction of liver enzymes, some drugs directly inhibit the action of enzymes (**enzyme inhibition**); this reduces the metabolism of other drugs taken at the same time that are metabolized by the same enzyme. In such cases, one would experience a much more intense or prolonged drug effect and increased potential for toxicity. Monoamine oxidase inhibitors (MAOIs), used to treat depression, act in the brain by preventing the destruction of certain neurotransmitters by the enzyme monoamine oxidase (MAO). The same enzyme is found in the liver, where it normally metabolizes amines such as tyramine, which is found in red wine, beer, some cheeses, and other foods. When individuals who are taking these antidepressants eat foods rich in tyramine, dangerous high blood pressure and cardiac arrhythmias can occur, making normal foods potentially life-threatening. Further detail on this side effect of MAOIs is provided in Chapter 18.

In addition, because MAOIs are not specific for MAO, they have the potential to cause adverse effects unrelated to MAO function. They inhibit several microsomal enzymes of the CYP450 family, producing elevated blood levels of many drugs and potentially causing increased side effects or unexpected toxicity.

A second drug–food interaction involves the ingestion of grapefruit juice, which significantly inhibits the biotransformation of many drugs metabolized by CYP450 3A4, including numerous psychiatric medications. A single glass (5 ounces) of grapefruit juice elevates the blood levels of those drugs significantly by inhibiting their first-pass metabolism. The effect is caused by chemicals in grapefruit that are not found in oranges, such as bergamottin. Inhibition persists for 24 hours and dissipates gradually after several days, but it can be a hazard for those taking medications daily, because it causes significant drug accumulation.

A second type of inhibition, based on **drug competition** for the enzyme, occurs for drugs that share a metabolic system. Because the number of enzyme molecules is limited, an elevated concentration of either drug reduces the metabolic rate of the second, causing potentially toxic levels. CYP450 metabolism of alcohol leads to higher-than-normal brain levels of other sedative–hypnotics (e.g., barbiturates or Valium) when administered at the same time, producing a potentially dangerous drug interaction.

Finally, differences in drug metabolism due to genetic and environmental factors can explain why some individuals seem to be extremely sensitive to certain drugs, but others may need much higher doses than normal to achieve an effect. Over 40 years ago, the first **genetic polymorphisms** (genetic variations among individuals that produce multiple forms of a given protein) for drug-metabolizing enzymes were identified. Large variations, for instance, were found in the rate of acetylation of isoniazid, a drug used to treat tuberculosis and subsequently found to relieve depression. Acetylation is a conjugation reaction in which an acetyl group is attached to the drug. These genetic polymorphisms that determine acetylation rate vary across populations. For instance, 44% to 54% of American Caucasians and African Americans, 60% of Europeans, 10% of Asians, and only 5% of Inuit are slow inactivators (Levine, 1973).

The enzymes that have been studied most are in the CYP450 family, and each has multiple polymorphisms. In that family, CYP2D6 (i.e., CYP450 2D6) is of great interest because it is responsible for metabolizing numerous psychotropic drugs, including many antidepressants, antipsychotics, antihistamines, muscle relaxants, opioid analgesics, and others. In a recent study, swabs of epithelial cells from the cheek linings of 31,563 individuals were taken and analyzed for the number of copies of the gene for CYP2D6. **FIGURE 1.12A** shows the distribution of samples based on the number (zero, one, two, or three or more) of normal CYP2D6 genes (Beoris et al., 2016; see Taylor et al., 2020, for review). A small percentage of individuals (0.14%) are very poor metabolizers and have multiple copies of a polymorphism that is ineffective in metabolizing substrates for the CYP2D6 enzyme. Intermediary metabolizers make up 7.25% of

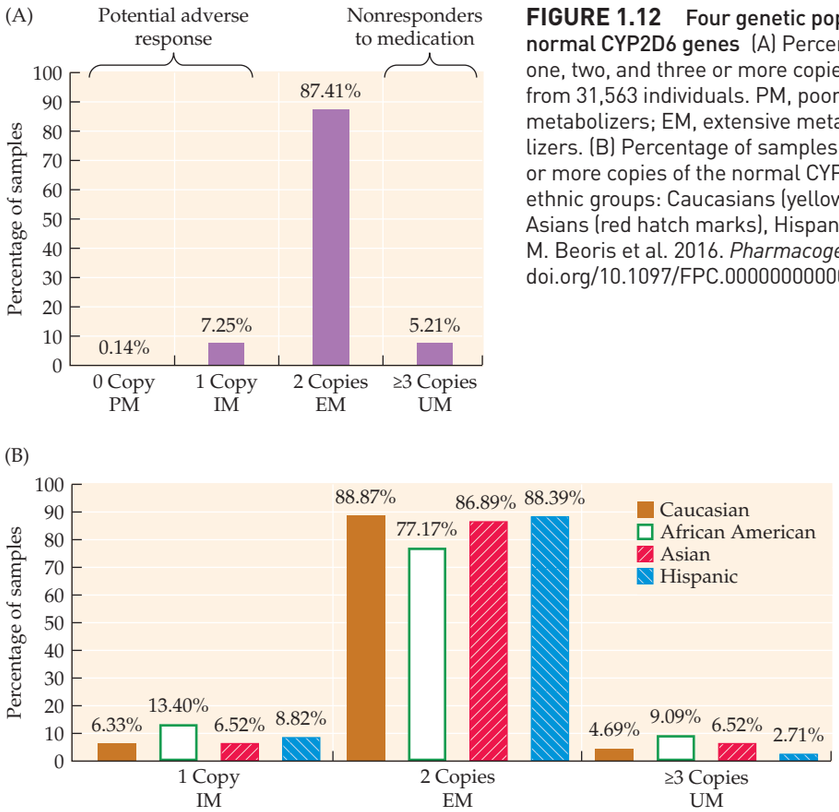

FIGURE 1.12 **Four genetic populations based on the number of normal CYP2D6 genes** (A) Percentage of samples containing zero, one, two, and three or more copies of the normal CYP2D6 gene from 31,563 individuals. PM, poor metabolizers; IM, intermediary metabolizers; EM, extensive metabolizers; UM, ultrarapid metabolizers. (B) Percentage of samples containing one, two, and three or more copies of the normal CYP2D6 gene in self-reported ethnic groups: Caucasians (yellow), African Americans (no-fill), Asians (red hatch marks), Hispanics (blue hatch marks). (After M. Beoris et al. 2016. *Pharmacogenet Genomics* 26 [2]: 96–99. doi.org/10.1097/FPC.0000000000000188)

the population tested and have one deficient allele and one normal allele. These two clusters of individuals having poorer metabolism would be expected to have greater bioavailability of those drugs, which may be responsible for adverse drug reactions or toxicity. These individuals would benefit from a reduction in drug dosage. Approximately 87% of the individuals are extensive metabolizers and have two normal alleles. They are considered extensive metabolizers because the normal enzyme is highly functional and efficient. The fourth group (5.21% of the population tested) are ultrarapid metabolizers and have multiple (three or more) normal gene copies. The ultrarapid group would be expected to have significantly lower blood levels of drug than normal, which may make them nonresponders to the medication. Hence, these individuals would benefit from higher drug dosage. Such differences are significant because there may be as much as a 1000-fold difference in rate of metabolism for a particular drug among these individuals. In addition, the data showed there are different distributions of these genotypes in different populations. **FIGURE 1.12B** shows the data for one or more copies of the normal gene (the samples with zero copies are not shown) broken down by self-reported ethnicity (about two-thirds of the individuals provided data on ethnicity). The data show that the frequency of individuals with two copies of CYP2D6 was significantly lower in African Americans than in the other ethnic groups and that the percentage of individuals with one copy was 1.5 to 2.1 times higher in that group. Additionally, the percentage of individuals with three or more copies among African American was 1.4 to 3.4 times higher. These differences indicate greater variation in CYP2D6 metabolism in African Americans, which puts some at greater risk for adverse side effects and others at risk for inadequate response to psychotropic medications. Further discussion of this topic can be found at the end of the chapter in the section Pharmacogenetics and Personalized Medicine.

Other enzymes also show wide genetic differences. For example, approximately 50% of certain Asian groups (Chinese, Japanese, and Koreans) have reduced capacity to metabolize acetaldehyde, which is an intermediary metabolic step in the breakdown of alcohol. The resulting elevation in acetaldehyde causes facial flushing, tachycardia, a drop in blood pressure, and sometimes nausea and vomiting. The reduced metabolic capacity is caused by a specific mutation in the gene for aldehyde dehydrogenase (Wall and Ehelers, 1995).

Along with variations in genes, other individual differences may influence metabolism. Significant changes in nutrition or in liver function, which accompany various diseases, lead to significantly higher drug blood levels and prolonged and exaggerated effects. Advanced

age is often accompanied by a reduced ability to metabolize drugs, while children under age 2 also have insufficient metabolic capacity and are vulnerable to drug overdose. In addition, both the young and the elderly have reduced kidney function, so clearance of drugs for them is much slower. Sex differences in drug metabolism also exist. For example, the stomach enzymes that metabolize alcohol before it reaches the bloodstream are far less effective in women than in men. This means that for an identical dose, a woman will have a much higher concentration of alcohol reaching her blood to produce biological effects. If you would like to read more about some of the clinical concerns related to differences in drug metabolism, see Applegate (1999).

RENAL EXCRETION Although drugs can be excreted from the body in the breath, sweat, saliva, feces, or breast milk, the most important route of elimination is the urine. Therefore, the primary organ of elimination is the kidney. The kidneys are a pair of organs, each about the size of a fist. They are responsible for filtering materials out of the blood and excreting waste products. As filtered materials pass through the kidney tubules, necessary substances such as water, glucose, sodium, potassium, and chloride are reabsorbed into the blood.

Most drugs are readily filtered by the kidney unless they are bound to plasma proteins or are of large molecular size. However, because reabsorption of water from the tubules makes the drug concentration greater in the tubules than in the surrounding blood vessels, many drug molecules are reabsorbed back into the blood. Ionization of drugs reduces reabsorption because it makes the drugs less lipid soluble. Liver biotransformation of drugs into ionized (water-soluble) molecules traps the metabolites in the kidney tubules, so they can be excreted along with waste products in the urine.

Reabsorption from the tubules, similar to diffusion across other membranes (discussed earlier), is pH-dependent. When tubular urine is made more alkaline, weak acids are excreted more rapidly because they become more ionized and are not reabsorbed as well; that is, they are "trapped" in the tubular urine. If the urine is acidic, the weakly acidic drug will be less ionized and more easily reabsorbed; thus, excretion will be less. The opposite is true for a weakly basic drug, which will be excreted more readily when tubular urine is acidic rather than basic. This principle of altering urinary pH is frequently used in the treatment of drug toxicity, when it is highly desirable to remove the offending drug from the body as quickly as possible. In the case of phenobarbital poisoning, for example, kidney excretion of this weakly acidic substance is greatly enhanced by alkalinization of the urine with sodium bicarbonate. This treatment leads to ionization and trapping of the drug within the tubules, from whence it is readily excreted. Acidifying the urine by administering IV ammonium chloride increases the percentage of ionization of weakly basic drugs, which enhances their excretion. For example, acidifying the urine increases the rate of excretion of amphetamine and shortens the duration of a toxic overdose episode.

Therapeutic drug monitoring

For a drug to be clinically effective while producing minimal side effects, optimal blood levels and hence drug concentration at the target site must be maintained throughout the treatment period. The difficulties in determining the appropriate drug dosage for initial clinical trials with humans and for veterinary medical treatment based on preclinical laboratory animal testing are described in **BOX 1.3**. Optimal blood levels must be determined in clinical trials before Food and Drug Administration (FDA) approval. However, wide variation in rates of absorption, metabolism, and elimination among individuals because of differences in gender, age, genetic profile, disease state, and drug interactions can lead to significant differences in blood levels. Blood levels that are too low prevent desired clinical outcomes, and for individuals with higher-than-normal blood levels, unwanted side effects and toxicity may occur. In the future, pharmacogenetic screening of individuals (see the section Pharmacogenetics and Personalized Medicine in Psychiatry) will allow personalized prescription of drug doses, but at present, the appropriate dosage of a drug is determined most often by the clinical response of a given individual. Under some conditions, such as for drugs with serious side effects, multiple blood samples are taken after drug administration to determine plasma levels of drug or to monitor a biological process (i.e., **biomarker**) for a toxic response (**therapeutic drug monitoring**). Short-term blood sampling may be done to establish the optimal dosage for a patient taking a new medication. After each dosage correction by the physician, it may take some time to reach steady state (approximately five half-lives), so monitoring may continue for several days or weeks, until the optimal dosage has been determined. For drugs that must be taken over the life span, periodic monitoring may be performed regularly. Monitoring detects changes in pharmacokinetics due to aging, hormonal changes during pregnancy and menopause, stress, changes in medical condition, or addition of new medications. Many of the monitored psychotropic drugs, such as antiepileptic drugs, including carbamazepine, some antidepressants, and drugs used as mood stabilizers such as lithium and valproic acid, are taken on a long-term basis.

Therapeutic drug monitoring is especially important for drugs that have a narrow therapeutic index (i.e., the dose needed for effectiveness is very similar to the dose that causes serious side effects; see section 1.2 Pharmacodynamics). Because blood levels rise to a peak and then

fall to a trough just before the next administration (see Figure 1.10), drug monitoring can ensure that the peak remains below the blood level associated with toxic effects, while the trough remains in the therapeutic range to maintain adequate symptom relief. Modifying the dosage for a given individual can optimize treatment. In addition, drug monitoring can be used to determine whether the individual is taking the drug according to the prescribed regimen. Failure to comply with the drug treatment protocol often can be corrected by further patient education. The American Association for Clinical Chemistry (2020) provides additional information on therapeutic drug monitoring at https://labtestsonline.org/tests/therapeutic-drug-monitoring.

BOX 1.3 ■ PHARMACOLOGY IN ACTION

Interspecies Drug Dose Extrapolation

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Interspecies drug dose extrapolation means converting or scaling the appropriate dose in one species to another species. It is vital not only in veterinary medicine, but also in drug development when the initial clinical trials with humans are based on preclinical testing in laboratory animals. It is also significant in the laboratory in order to replicate results from one species in another. The goal of dose extrapolation is to find the optimal dose for effectiveness and safety. See Sharma and McNeill (2009) for a full discussion.

Comparing the sizes of the animals is the most obvious approach to scaling a drug dose to a different species, but it is not the only factor. Using size alone can have disastrous consequences, as shown by the tragic outcome in Tusko, a 14-year-old Asiatic elephant housed in the Lincoln Park Zoo in Oklahoma City (West et al., 1962). The researchers used only the difference in weight to scale the dose for the elephant from previous experiments with cats. If the elephant's sensitivity to the hallucinogenic lysergic acid diethylamide (LSD) resembled that of humans, the 297 mg given to the elephant would have been an enormous overdose. Almost immediately after the drug was injected into the rump of the 3.5-ton elephant with a dart rifle, he stormed around his pen, appearing uncoordinated before he collapsed, defecated, and had continuous seizures. His tongue turned blue and he struggled to breathe, dying shortly later of strangulation. There were efforts to save him, but the drugs used may have instead contributed to his death. One must conclude that the elephant's sensitivity to LSD more closely resembled that of humans than of felines.

There are many pharmacokinetic and pharmacodynamic factors that are unrelated to size yet vary significantly among species. For example, protein binding at silent depots varies greatly among species because of differences in affinity to and number of binding sites. Hence, for any drug that shows high depot binding in one species, using weight alone to determine dose would be ineffective, whereas correction for the extent of protein binding would increase accuracy. Complex interspecies differences in drug metabolism are also key factors in differences in bioavailability of a given drug. For example, there are major variations among species in the CYP450 enzyme family amino acid sequences. The varied enzyme structures determine which drug substrates are acted upon by the enzyme. Another example of varied metabolism is conjugation with glucuronide, which is important and efficient in humans, while cats lack glucuronidation. Rats are very efficient acetylators, but dogs lack acetylation, while humans are intermediate between the two. It is clear that these differences will lead to variations in the blood levels of drug in different species.

In addition to differences in weight and pharmacokinetic factors, drug targets also contribute to variations in interspecies response to administered drugs. CNS neurotransmitters are differentially distributed in the brains of various species, and differences in the number, affinity, distribution, and regulation of receptors likely explain dramatic differences in drug response. For example, opiate analgesics such as morphine cause CNS depression in primates, dogs, and rats but induce excitation in horses and cats. These pharmacodynamic factors are not related to the size of the animal, so to adequately convert the drug dose, one should have some understanding of the receptor characteristics of each species.