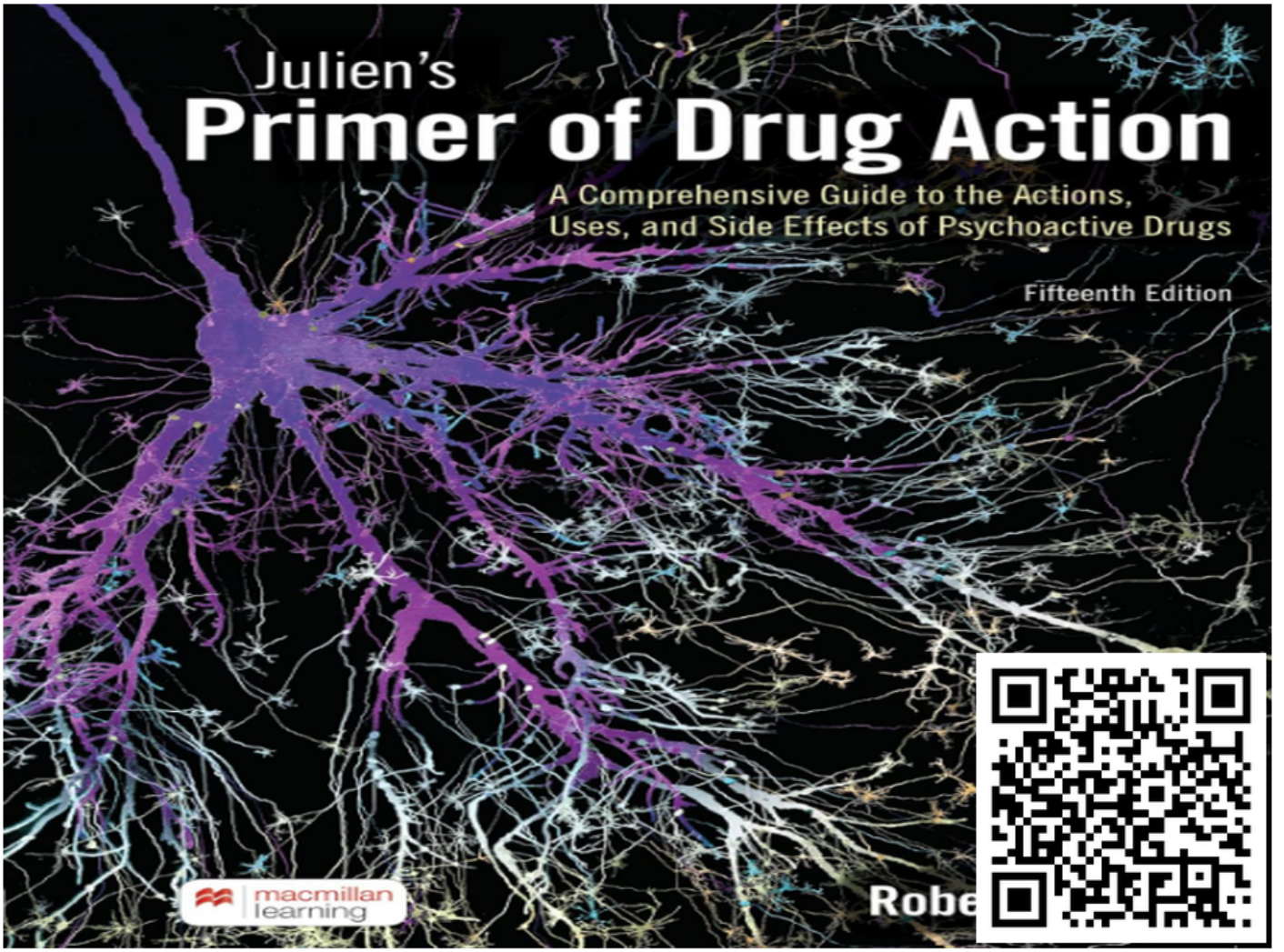

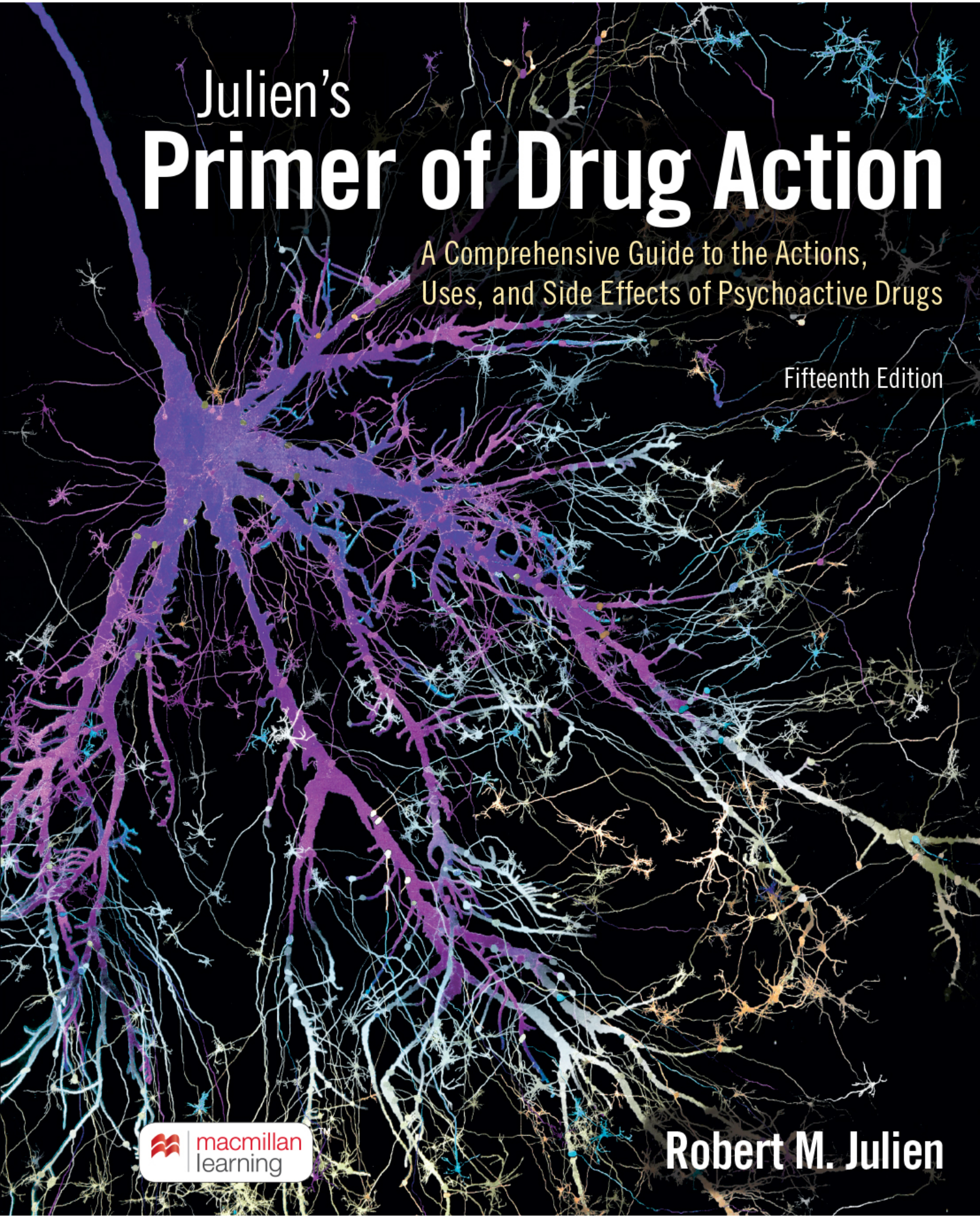
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A Comprehensive Guide to the Actions, Uses, and Side Effects of Psychoactive Drugs
Fifteenth Edition
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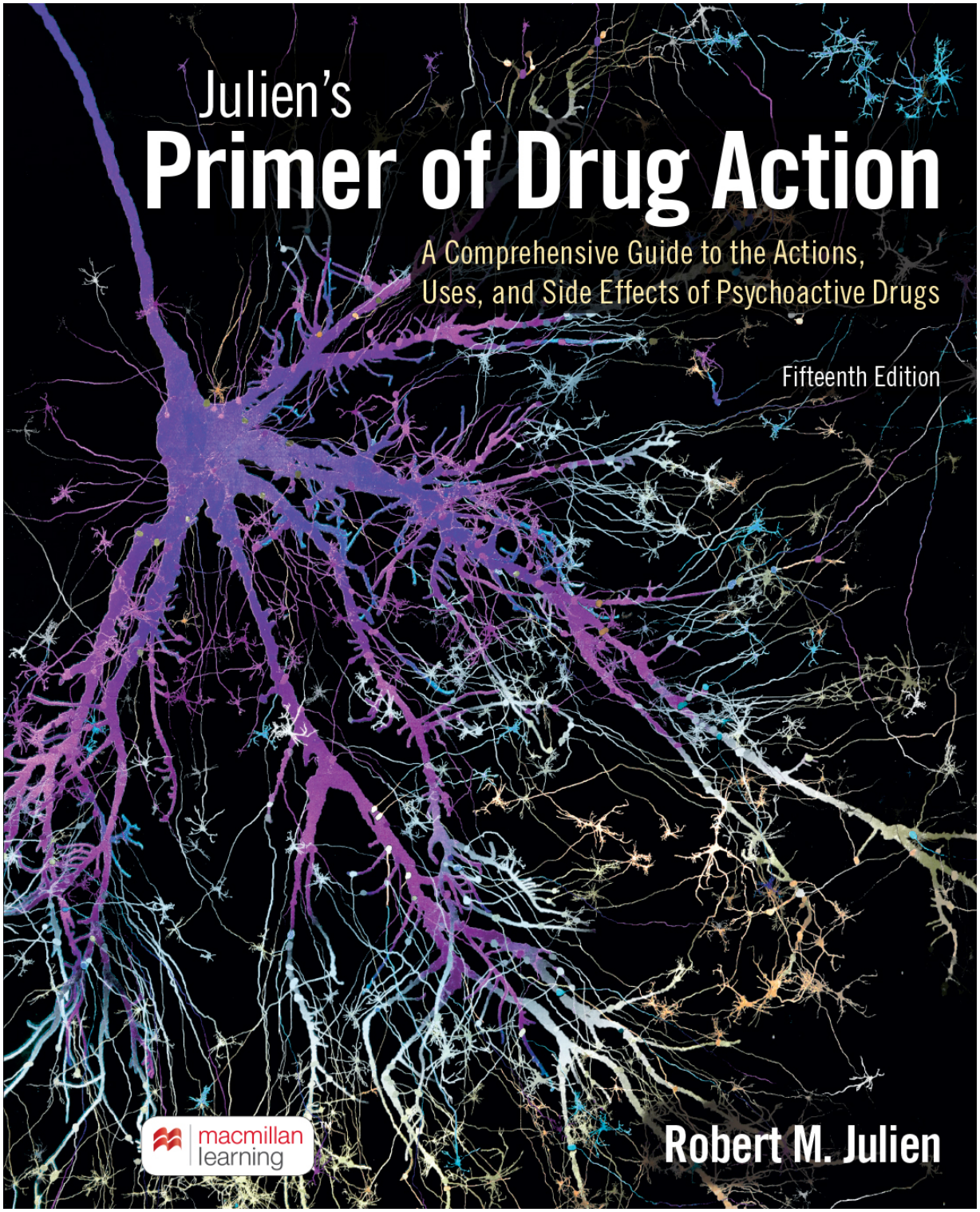
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Julien’s Primer of Drug Action

Julien's Primer of Drug Action

A Comprehensive Guide to the Actions, Uses, and Side Effects of Psychoactive Drugs

Fifteenth Edition

Robert M. Julien, M.D., Ph.D.
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with

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Robert M. Julien received his Ph.D. in pharmacology from the University of Washington and his M.D. from the University of California at Irvine. His many research articles focus on the psychopharmacology of sedative and antiepileptic drugs. Formerly an associate professor of pharmacology and anesthesiology at Oregon Health Sciences University, Dr. Julien is retired as staff anesthesiologist at St. Vincent Hospital and Medical Center in Portland, Oregon. For almost five decades, Dr. Julien has been taking on and bringing to completion the herculean task of revising each edition of *Julien's Primer of Drug Action* to maintain its succinct yet comprehensive and clear presentation of the most up-to-date advances in psychopharmacology. He remains active as a psychopharmacology consultant.

Claire Advokat, Ph.D., is a professor emerita in the Department of Psychology at Louisiana State University. **Joseph Comaty, Ph.D.**, formerly served as chief psychologist in the division of quality management of the Louisiana State Office of Behavioral Health and adjunct professor of psychology at Louisiana State University. He is licensed to prescribe psychotherapeutic drugs in the state of Louisiana. Both Dr. Advokat and Dr. Comaty remain on the faculty of the Postdoctoral Master of Science program in Clinical

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Brief Contents

Contents

Preface

As a youth I spent considerable time in my father's pharmacy in Seattle. I remember being fascinated by the question of why someone would purchase aspirin to treat a headache or obtain a prescription for Dilantin in order to prevent seizures. Understanding the mechanism of "why" a drug might effectively do something was a childhood fantasy, but it became a deeply engrained ambition. Eventually, I obtained a Ph.D. in pharmacology at the University of Washington. I became a professor at the University of California at Irvine and directed a psychopharmacology laboratory, studying epilepsy, antiepileptic drugs, and hypnotic drugs. In 1977, I completed my M.D. at UC Irvine and then became a professor of pharmacology and anesthesiology at Oregon Health Sciences University, followed by a 25-year clinical practice as an anesthesiologist at a large community hospital in Portland. Through all this I wrote extensively, taught pharmacology and anesthesiology, and eventually traveled extensively teaching psychopharmacology.

The story of the origin of this book actually began on November 13, 1971. At that time, I was a young professor at UC Irvine teaching and conducting psychopharmacology research. Tragically, a plane crash took the lives of three football coaches from a neighboring college,

California State College, Fullerton, along with the pilot of the plane. As a result of the crash, that college was left without teachers for their winter classes. They asked UC Irvine for assistance. I agreed to teach one of their scheduled courses in drug education, starting in January 1972. Following the course, I complained to a senior colleague that I had no materials from which to teach. I naively stated that someone ought to write a book on psychopharmacology. A few weeks later I received in the mail a contract from his publisher. I signed the contract and wrote what turned out to be the first edition of this book. Since then, updated and expanded editions have appeared about every three years.

Thus, counting my boyhood experiences in my father's pharmacy, I have been a witness to the evolution of psychopharmacology for 70 years, from its earliest days in the 1950s to the present. This lifelong passion for psychopharmacology is what led me to embark on this 15th edition of *Julien's Primer of Drug Action*.

As in each of the prior editions, I strive in this 15th edition to present the latest developments in psychopharmacology as clearly and concisely as I can, describing the general principles of structure and mechanisms of action of each class of psychoactive drugs, as well as providing specific information about the individual agents. Also like prior editions, this edition is divided into four parts: (1) Chapters 1–3 provide an introduction to the basics of psychopharmacology; (2) Chapters 4–10 cover the concept of addiction and the various kinds of drugs of abuse; (3) Chapters 11–14

cover the different classes of psychotherapeutic drugs; and (4) Chapters 15–18 cover the uses and effects of psychoactive drugs in special populations (pregnant women, children and adolescents, and older adults), ending in Chapter 18 with a review of psychopharmacology in the context of the COVID-19 pandemic and with a look into the future of the field.

The chapters on drugs of abuse provide historical context and epidemiological updates, discussions of the classic agents, and descriptions of the most recent drugs of concern, as well as the latest developments in regard to pharmacological treatments of the disorders associated with abuse of these drugs. Each chapter on psychotherapeutic drugs includes an overview of the disorders for which the drugs are indicated, discussion of the mechanisms of action of the drugs, and discussion of the rationales for drug treatment.

Certainly, there is overlap between the therapeutic and addictive effects of drugs. Many types of therapeutic drugs, such as the stimulants, benzodiazepines, and opiates, are involved in the ongoing epidemic of abuse and overdose deaths. Extraordinary efforts are being made to develop products that are resistant to misuse and to diversion into illicit channels of distribution. At the same time, research on substances primarily considered to be drugs of abuse (such as the psychedelic drugs and cannabis) is exploring new therapeutic possibilities. As always, we psychopharmacologists are optimistic that scientific investigation will result in new insights

into the etiology of mental illness and addiction and that the future will bring more effective treatments for these devastating disorders.

In the years since the 14th edition, societal interest in psychopharmacology has continued to increase. New features and focuses that characterize this 15th edition reflect the following factors involved in this increasing interest:

- The opioid crisis has resulted in hundreds of thousands of deaths, a majority of which followed from the adulteration of opioid products with fentanyl and potent fentanyl derivatives.
- Rapid-acting opioid antagonists are now widely available.
- Increasing public acceptance of medical and recreational marijuana, cannabidiol (CBD), and other cannabis products has accompanied changes in their legal status.
- Pharmacological management of opioid and alcohol dependence has gained increasing interest.
- New antipsychotic medications with off-label uses continue to appear commercially.
- New products for the treatment of bipolar depression have also continued to appear.
- Psychedelic psychopharmacology has expanded widely, including with an increasing therapeutic use of psychedelic drugs for treatment of pain and depression.
- Psychotherapeutic drugs for treatment-resistant depression have become an expanding focus of research.

- Medications to treat personality and other disorders have also gained increasing interest.
- The treatment of cognitive dysfunction in Alzheimer's disease — both its promises and its failures — continues to be a focus of research.
- Off-label uses of psychoactive medications continue to expand.
- The COVID-19 pandemic has had profound effects on our society, including effects on mental health and long-term effects of having been infected with the virus.

Finally, a word about a new feature in this edition, **Dr. J's Musings**: it is my privilege to share some of my "musings" about events that have occurred during my long career in psychopharmacology. I hope that the reader will find them interesting, informative, and perhaps even entertaining.

Acknowledgments

The editorial work of Len Neufeld and Stephanie Ventura on this 15th edition has been marvelous, as has the support of Senior Executive Program Manager and Editor Christine Cardone, reflecting her commitment to this project. I am also indebted to Drs. Joe Comaty and Claire Advokat, who authored the 13th and 14th editions of this text; without their work, this new edition would not have been possible.

Finally, I am indebted to the instructors who have provided insightful feedback for this 15th edition, especially Michael Hylin of Southern Illinois University, who provided excellent feedback on the *Did You Know* boxes. Reviewers included:

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Julien’s Primer of Drug Action

Part 1
Introduction to Psychopharmacology: The Biological Basis of Drug Action

A **drug** is a chemical substance used for its effects on bodily processes. **Pharmacology** is the science of *how* drugs affect living organisms; **psychopharmacology**, more specifically, is the study of how drugs affect the brain and behavior. To understand the actions, behavioral uses, therapeutic uses, and abuse potentials of **psychoactive drugs** — chemical substances that alter mood or behavior as a result of alterations in the functioning of the brain — it is helpful to know how the body responds to the presence of such drugs. This understanding involves the basic principles of drug absorption, distribution, metabolism, and elimination as well as the interactions of drugs with their receptors, the interactions that produce the effects of drugs.

As an introduction to psychopharmacology, this book presents not only drugs useful in treating psychological disorders, but also drugs prone to compulsive use and abuse. Before discussing specific drugs or classes of drugs, it is necessary to discuss fundamentals of drug action common to all drugs.

Chapter 1 explores **pharmacokinetics**, the movement of drug molecules into, through, and out of the body. It addresses such questions as these: What are the ways by which drugs get into the body and how does that relate to their actions? Once in the body, how do drugs get to the sites at which they produce their effects? Once a drug exerts its effect, how is that action terminated? Finally, how does the body eventually get rid of the drug?

For readers without a background in neuroscience, Chapter 2 introduces the structure and function of the nervous system and the neuron, because this is where psychoactive drugs produce their effects. We focus on the synapse (the connection between two different neurons) and on neurotransmitters, the chemical substances through which neurons communicate. By studying the process of synaptic transmission, we begin to understand the mode of action of psychoactive drugs. The phenomenon of synaptic transmission is not static; rather, neurons have the ability to remodel themselves continually, a process called **synaptic plasticity**, which mediates learning and memory as well as such disorders as anxiety, depression, and addiction. A healthy, functioning brain is one that through this process of synaptic plasticity is continually remodeling itself in response to the environment. Healthy neurons continually form new synaptic contacts, maintaining the beautiful architecture built through normal interactions with millions of other neurons.

Chapter 3 explores **pharmacodynamics**. It examines the interaction between drugs and the **receptors** to which the drugs attach and through which they produce their effects. We describe receptors both structurally and functionally, and we discuss how drugs alter receptor structure and function. Finally, we summarize the ways in which such actions underlie the therapeutic effects and the side effects of drugs. These three chapters provide the basic foundation for understanding the more specific information in subsequent chapters.

Chapter 1
Pharmacokinetics: How the Body Handles Drugs

Chapter Outline

When we have a headache, we take it for granted that after taking some aspirin our headache will probably disappear within 15 to 30 minutes. We also take it for granted that, unless we take more aspirin later, the headache may recur within 3–4 hours. This aspirin

scenario illustrates the four basic processes in pharmacokinetics (collectively referred to as ADME):

1. ***A****bsorption* of the aspirin into the body from the swallowed tablet
2. ***D****istribution* of the aspirin throughout the body and the brain, including into the fetus if a pregnant female has taken the drug
3. ***M****etabolism* as the aspirin that has exerted its analgesic effect is broken down into metabolites (by-products or waste products) that no longer exert any effect
4. ***E****limination* of the metabolic waste products, usually in the urine

In concert, these four processes determine the **bioavailability** of a drug at its receptors — that is, how much of the drug that is administered actually reaches its target and how long it persists there.

The goal of this chapter is to introduce these pharmacokinetic processes. Because many drugs need to be taken chronically and for various periods of time, the chapter also explores the steady-state maintenance of therapeutic blood levels of drugs in the body and the usefulness of therapeutic drug monitoring. Finally, the chapter introduces the concepts of drug tolerance and drug dependence, concepts that become very important as certain classes of drugs (e.g., opioids) are discussed later in the book.

DR. J'S MUSINGS 1.1

Can I Have Dessert Without Eating My Vegetables?

Beginning in the 1960s, the continuing explosion in drug development, clinical research, and medication approvals for mental health disorders has made this the most exciting period in the history of pharmacology. How to share this excitement has always been a challenge. Many educators immediately delve into marijuana, opioids, hallucinogens, and stimulants. However, I have long been convinced that understanding the basics makes it easier to understand the actions of *all* drugs, including psychoactive drugs — hence this opening chapter on pharmacokinetics. It is a bit like eating your vegetables before eating dessert — not fun, but necessary for good nutrition. In other words, it's useful to learn the basics of how drugs work in general before delving into the actions of specific drugs.

Usually, the time course of a particular drug's actions — the time to onset and the duration of effect — simply reflects the amount of time required for the rise and fall of the drug's concentration at the target site. Figure 1.1 summarizes drug movement through the body to its site of action, where it produces a pharmacological response, and then to the kidneys where the drug and its metabolites are excreted in urine.

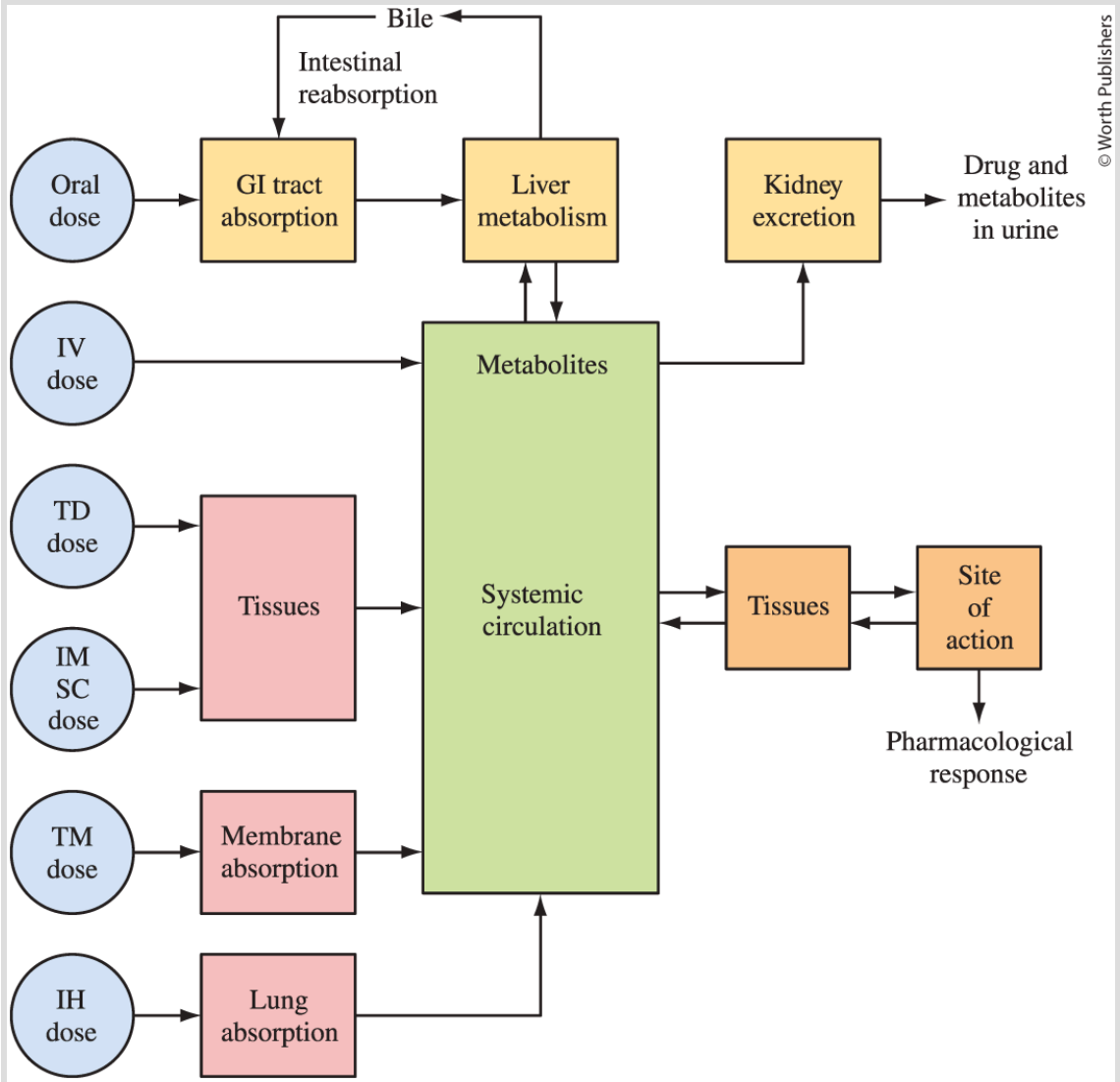

FIGURE 1.1 The Fate of a Drug in the Body. IV = intravenous; TD = transdermal; IM = intramuscular; SC = subcutaneous; TM = transmembrane; IH = inhalational.

The root *kinetics* in the word *pharmacokinetics* implies both movement and time. Knowledge of movement and time offers significant insight into the action of a drug. At the very least, it helps distinguish a particular drug from related drugs. For example, the main difference between the two benzodiazepine sedatives

lorazepam (Ativan)[1] and triazolam (Halcion) is in their pharmacokinetics. Both of these drugs have sedative and antianxiety effects. Lorazepam, however, persists in the body for at least 24 hours, while triazolam persists for only about 6–8 hours. If lorazepam is taken at bedtime for treatment of insomnia, daytime sedation the next day can be a problem because lorazepam persists in the body through the next day. But for treating anxiety, where a longer, steady action might be useful, lorazepam would work better than triazolam.

The kinetic differences between lorazepam and triazolam are illustrated in Figure 1.2, which shows three ranges in the blood plasma: an ineffective range (where not enough drug is present to produce either sedative or antianxiety effect), a therapeutic range, and a toxic range (where sedation becomes excessive). Triazolam reaches peak blood level rapidly and stays in the therapeutic range for only a short time. Lorazepam, in contrast, reaches peak blood level more slowly and persists longer in the therapeutic range. In essence, pharmacokinetic differences between the two drugs account for these results and allow two similar drugs to be used to achieve different therapeutic goals.

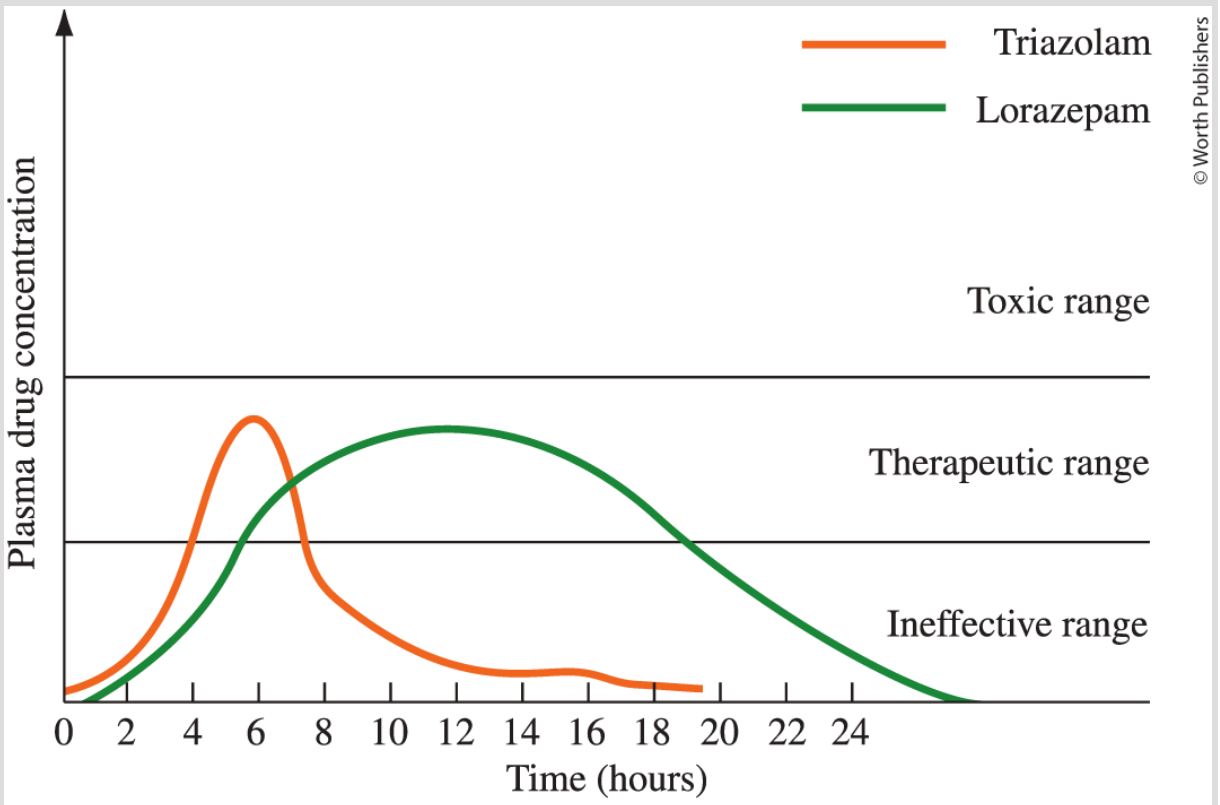

FIGURE 1.2 Theoretical Blood Levels of Triazolam and Lorazepam Following Oral Administration. Triazolam is a short-acting benzodiazepine, and lorazepam is a longer-acting benzodiazepine.

DR. J'S MUSINGS 1.2

How ADME Can Work for You

If you remember to consider the acronym ADME when you study a drug, you'll get a brief overview of how the drug is handled by the body:

- *Absorption* is usually oral, unless the drug must be given as an injection
- *Distribution* of most psychoactive drugs is in the blood, to reach the brain
- *Metabolism* breaks the drug down, usually into inactive by-products
- *Elimination* is the excretion of these by-products in urine

Drug Absorption

The term **drug absorption** refers to processes and mechanisms by which drugs pass into the bloodstream (usually from the stomach and intestine). For any drug, a route of administration, a dose of the drug, and a dosage form (liquid, tablet, capsule, injection, patch, spray, or gum) must be selected that will both place the drug at its site of action in a pharmacologically effective concentration and maintain the concentration for an adequate period of time. **Drug administration** is most often oral (the drug is swallowed when taken by mouth) and the drug then passes into the blood through absorption from the stomach and GI tract. A drug can also be administered for absorption through the membranes of the GI tract by embedding the drug in a suppository, which is placed in the rectum. Drugs can also be administered by the following routes, which bypass the GI tract:

- Inhalation (breathed in through the lungs as gases, vapors, or particles carried in smoke or in an aerosol)
- Absorption through mucous membranes (from "snorting," or sniffing, the drug, with the drug being deposited on the oral or nasal mucosa)
- Absorption through the skin (usually via a drug-containing skin patch)
- Injection (given in liquid form with a needle and syringe)

Oral Administration

To be effective when administered orally, a drug must be soluble (able to dissolve) and stable in stomach fluid (not destroyed by gastric acids), must penetrate the lining of the stomach or enter the intestine and penetrate the intestinal lining, and must then pass into the bloodstream. Because they are already in solution, drugs that are administered in liquid form tend to be absorbed more rapidly than those given in solid form in a tablet or capsule. When a drug is taken in solid form, both the rate at which it dissolves and its chemistry limit the rate of absorption. Food in the stomach usually tends to slow the rate of absorption. Rarely, an oral formulation contains a precursor of a drug, called a **prodrug**, rather than the active drug itself. A prodrug must undergo chemical conversion by metabolic processes in order to become an active pharmacological agent. One example of this type of medication is the drug lisdexamfetamine (Vyvanse), approved for the treatment of attention deficit/hyperactivity disorder (ADHD) (discussed in Chapter 16).

After a tablet dissolves, the drug molecules contained within it are carried into the upper intestine, where they are absorbed across the intestinal mucosa by a process of passive diffusion — that is, passing from an area of high concentration into an area of lower concentration. This process necessitates that the drug molecules, at least to some degree, be lipid soluble (soluble in fat). In reality, even a small amount of **lipid solubility** allows for absorption after oral administration; drugs that are more lipid soluble are merely

absorbed faster than those that are less lipid soluble. Most psychoactive drugs have good solubility in the lipid linings of the stomach and intestine; typically, about 75% (or more) of the amount of an orally administered psychoactive drug is absorbed into the bloodstream within 1–3 hours after administration.

As illustrated in Figure 1.3, nutrients (and orally administered drugs) absorbed from the small intestine flow into veins for fairly even distribution throughout the body. As part of this distribution process, venous blood (containing drugs that were absorbed) passes in the portal vein to the liver, where most drug metabolism takes place. Unmetabolized drug then passes through the liver and into the general circulation and into all body compartments, including the brain.

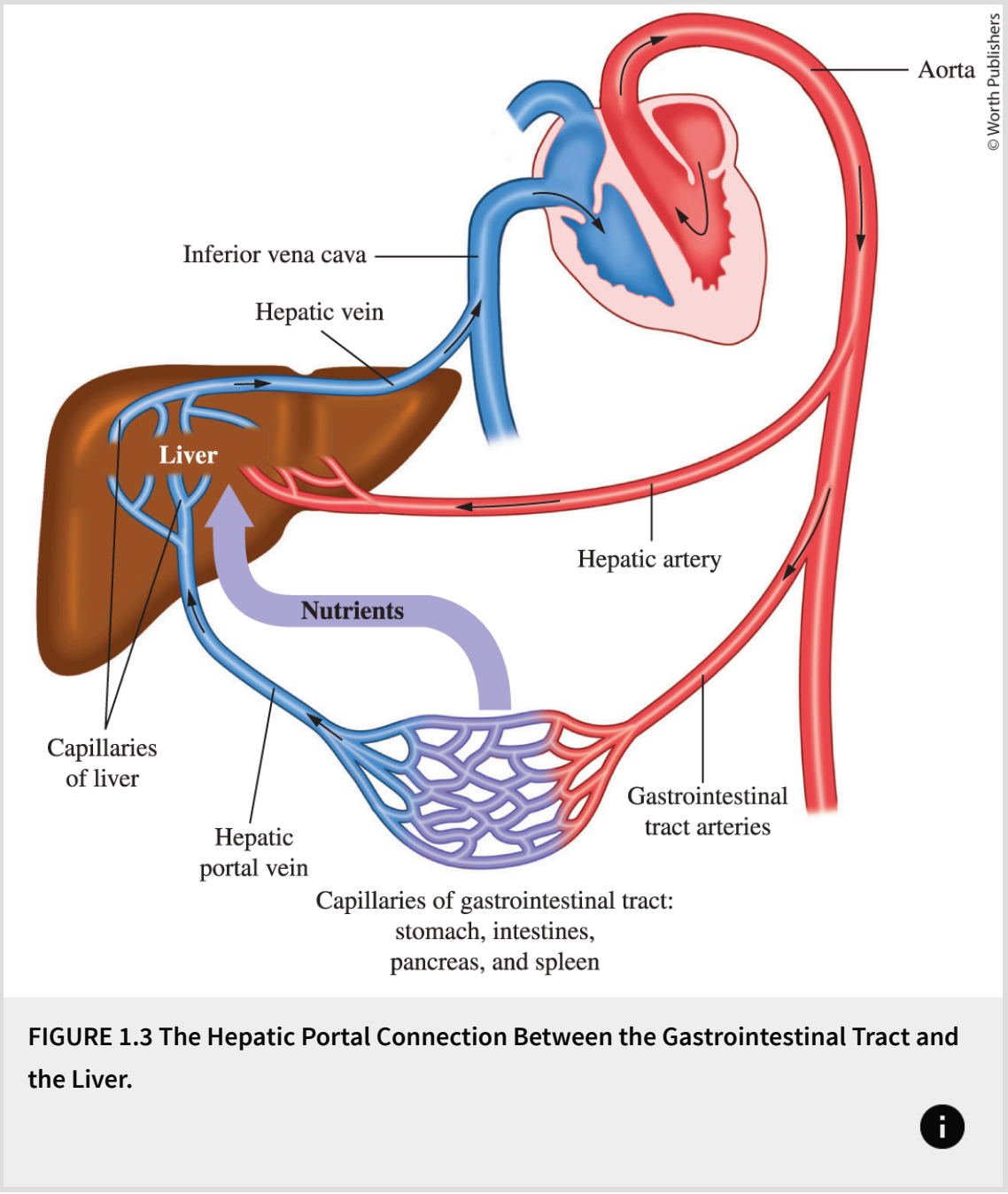

FIGURE 1.3 The Hepatic Portal Connection Between the Gastrointestinal Tract and the Liver.

There are some exceptions to this general rule. One involves buspirone (BuSpar), an antianxiety drug that has limited clinical efficacy, primarily because an enzyme called CYP-3A4, located in the walls of the stomach lining, rapidly metabolizes most of it, reducing the oral absorption of buspirone by over 90%. Should

buspirone be taken with grapefruit juice, however, a component in the juice (furanocoumarin) inhibits the CYP-3A4 enzyme, allowing the buspirone to be more completely absorbed, which increases its blood concentration and thus affects both its therapeutic utility and its toxicity.

More broadly, grapefruit and other juices taken with certain medications increase drug absorption and may increase the toxicity of those drugs. A review of multiple clinical studies on such interactions identified 22 juice-drug combinations of clinical relevance (Chen et al., 2018).

Although oral administration of drugs is common, it does have disadvantages. First, it may occasionally lead to vomiting and stomach distress. Second, although the amount of a drug that is put into a tablet or capsule can be calculated, how much of it will be absorbed into the bloodstream cannot always be accurately predicted because of genetic differences among people (in the amount and composition of the enzymes they have that metabolize the drugs) and because of differences in the manufacture of the drugs. Finally, the acid in the stomach destroys some orally administered drugs, such as local anesthetics and insulin, before they can be absorbed. To be effective, those drugs must be administered by injection.

Rectal Administration

Drugs are administered rectally (usually in suppository form) if the patient is vomiting, unconscious, or unable to swallow. However, absorption after rectal administration is often irregular, unpredictable, and incomplete, and many drugs irritate the membranes that line the rectum.

Administration by Inhalation

Inhalation is a popular method of administration of recreational drugs such as nicotine in tobacco cigarettes and vapors, tetrahydrocannabinol (THC) in marijuana, heroin when smoked, crack cocaine, ice methamphetamine, and the various inhalants of abuse, all of which are discussed later in this book. In addition, certain therapeutic drugs are effectively administered by inhalation, such as bronchodilators (used to treat asthma) and certain general anesthetics. The use of inhalation as a route of administration follows from two observations:

1. Lung tissues have a large surface area through which large amounts of blood flow, allowing for rapid absorption of drugs from the lungs into the blood (often within seconds).
2. Drugs absorbed into pulmonary (lung) capillaries are carried in the pulmonary veins directly to the left side of the heart (the arterial side, as shown in Figure 1.4) and from there directly into the aorta and the arteries carrying blood to the brain. As a

result, drugs administered by inhalation may have an even faster onset of effect than drugs administered intravenously, with an intense effect that may promote compulsive use.

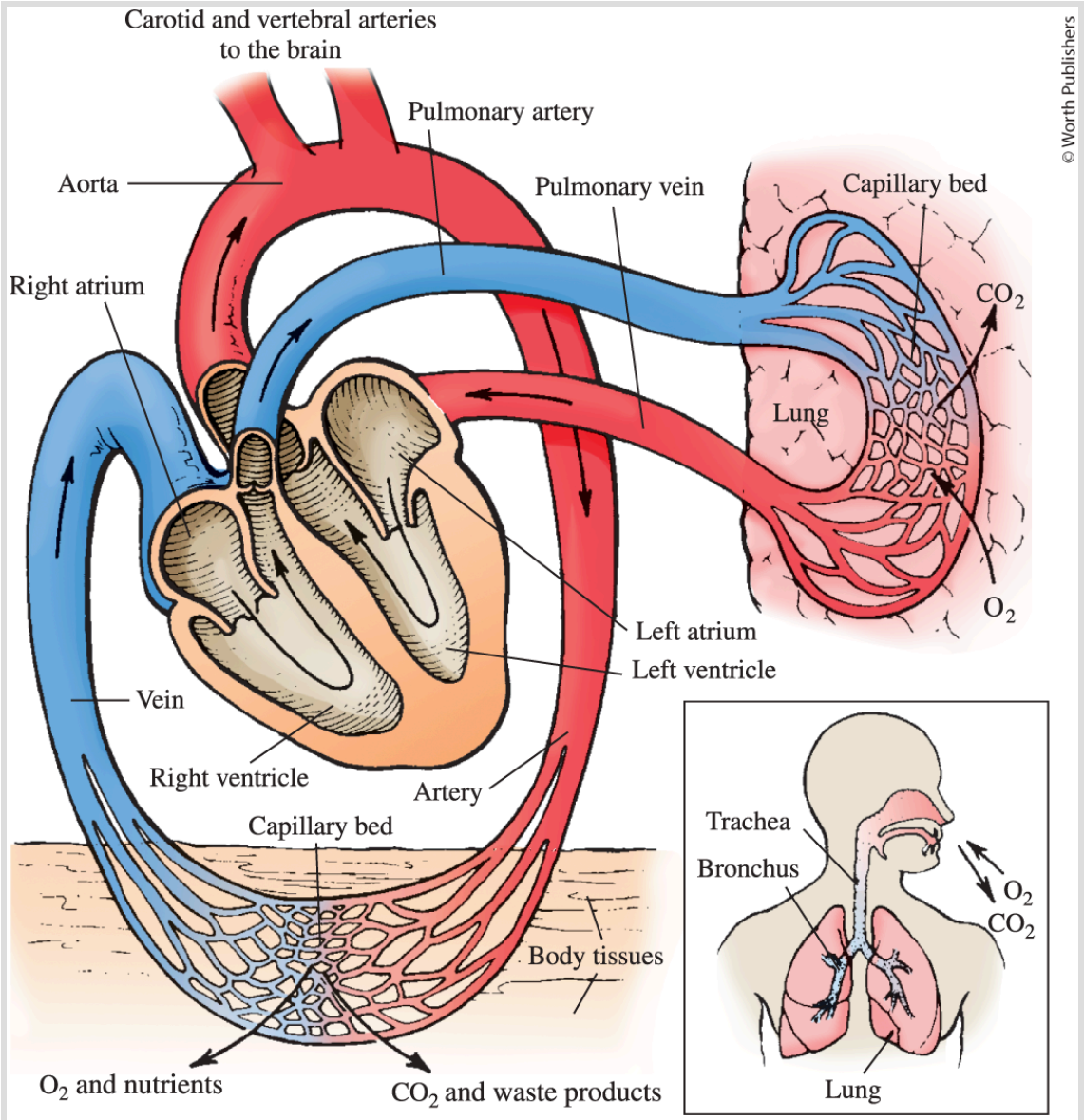

FIGURE 1.4 Heart and Circulatory System. Blood returning from the systemic venous circulation to the heart enters the right atrium and flows into the right ventricle. With contraction of the heart, this blood is pumped into the pulmonary arteries leading to the lungs. Once the blood is in the pulmonary capillaries, carbon dioxide (CO_2) is lost and replaced by oxygen. The oxygenated blood returns to the heart in the pulmonary

veins, which empty into the left atrium, from which the blood flows into the left ventricle. With heart contraction, the oxygenated blood is pumped from the left ventricle into the aorta and is carried throughout the body. In the systemic capillary beds, oxygen and nutrients are supplied to the body tissues and brain through the walls of the capillaries, while CO_2 and other waste products are returned to the blood. The CO_2 is eliminated through the lungs, and the other waste products are metabolized in the liver and excreted in the urine.

Administration Through Mucous Membranes

Occasionally, drugs are administered through the mucous membranes of the mouth or nose. Here are a few examples:

- Cocaine powder, when sniffed, adheres to the membranes on the inside of the nose and is absorbed directly into the bloodstream. (Cocaine is discussed in Chapter 7.)
- Nicotine in snuff, nasal spray, and chewing gum formulations is absorbed through the mucosal membranes directly into the bloodstream. (Nicotine is discussed in Chapter 6.)
- Since 1998, the opioid narcotic fentanyl (Sublimaze) has been available in lollipop form for use before and after surgery on children. This allows this pain-relieving drug to be provided without subjecting children to a painful injection. As the lollipop is sucked, the drug is released and absorbed through the mucous membranes of the mouth. This form of administering fentanyl has also become popular for patients

with disabling pain when orally administered pain relievers are insufficient and injection of opioid narcotics is too painful. (Fentanyl is discussed in Chapter 10.)
- A sublingual (placed under the tongue) combination of buprenorphine (an opioid narcotic) and naloxone (an opioid antagonist) is available for the office-based treatment of opioid dependency. (This is also discussed in Chapter 10.)

Administration Through the Skin

Over the past several years, several medications have been incorporated into **transdermal patches** that adhere to the skin. A transdermal patch is a bandagelike therapeutic system that provides continuous, controlled release of a drug from a reservoir through a semipermeable membrane. The drug is slowly absorbed into the bloodstream at the area of contact. Here are some examples of drugs that can be administered in this way:

- Nicotine (used to deter smoking behaviors)
- Fentanyl (used to treat chronic pain)
- Clonidine (used to treat hypertension)
- Estrogen or other hormones (used to replace reduced hormones in postmenopausal women or for contraception)
- Scopolamine (used to prevent motion sickness)
- Buprenorphine (Butrans, used to treat opioid dependence)
- Selegiline (Emsam, used to treat depression)
- Methylphenidate (Daytrana, used to treat ADHD in children)

- Rivastigmine (used to treat Alzheimer's disease)

All these transdermal skin patches allow for slow, continuous absorption of the drug over hours or even days, potentially minimizing side effects associated with rapid rises and falls in plasma concentrations of the drug.

Administration by Injection

Administration of drugs by injection can be done by **intravenous injection** (directly into a vein), **intramuscular injection** (directly into a muscle), or **subcutaneous injection** (just under the skin). Each of these routes of administration has its advantages and disadvantages (see Table 1.1).

TABLE 1.1 Some Characteristics of Drug Administration by Injection

Route	Absorption Pattern	Special Utility	Limitations and Precautions
Intravenous	Immediate absorption Avoids unpredictability of absorption after oral administration	Valuable for emergency use Permits extremely precise dosage Permits dilution of drug for administration of large volumes or irritating substances	Increased risk of adverse effects Solutions must usually be injected slowly Not suitable for oily solutions or insoluble substances