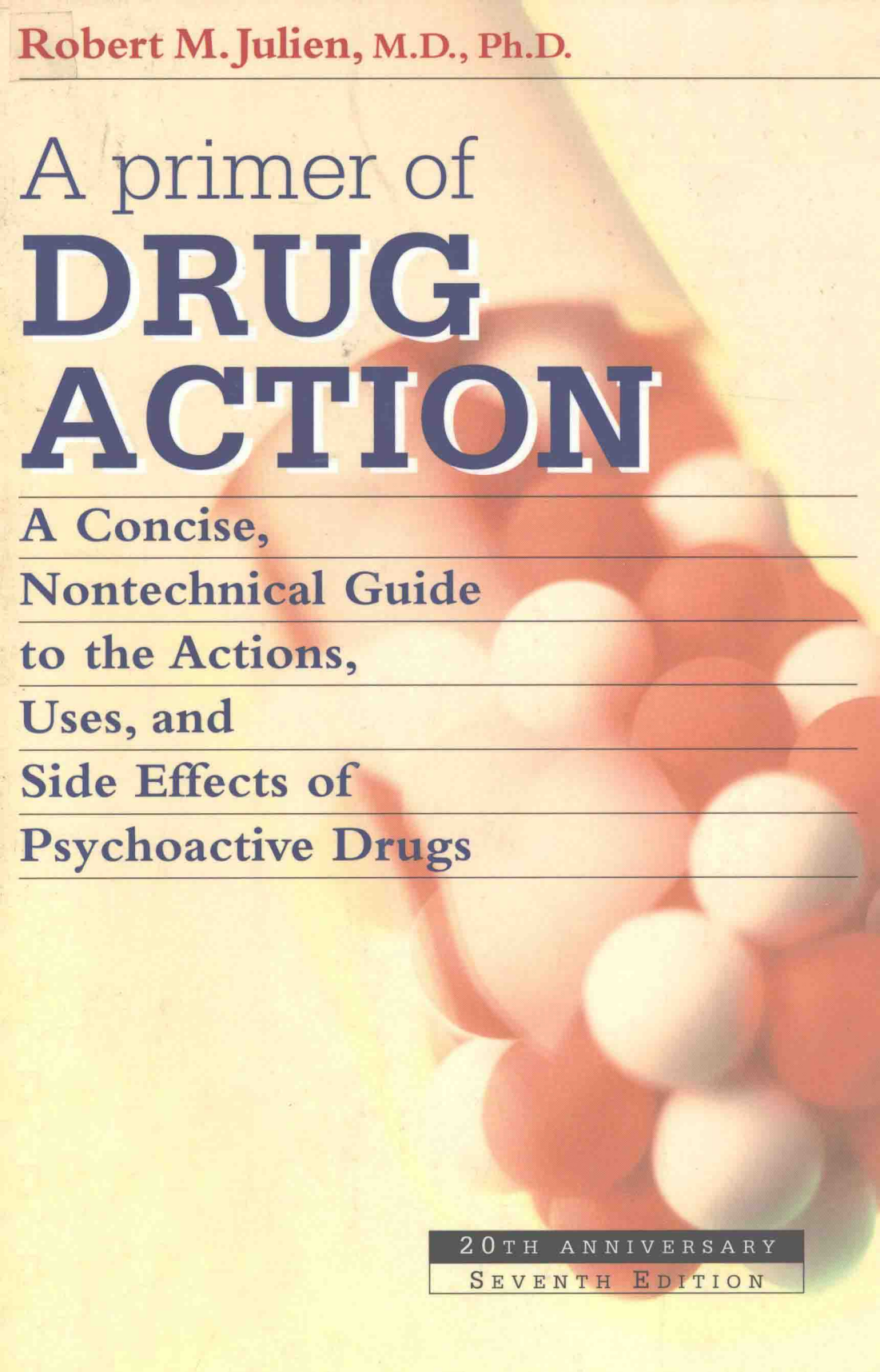
Robert M. Julien, M.D., Ph.D.

A primer of DRUG ACTION

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



20TH ANNIVERSARY
SEVENTH EDITION

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PREFACE

In the 20 years since the publication of the first edition of *A Primer of Drug Action* there has been an explosion of knowledge about psychoactive drugs, their use in the treatment of mental dysfunction, and their potential for misuse. In 1975, drug abuse was generally of more interest than was psychopharmacotherapy (the use of drugs to treat psychological disorders). Today, however, although drug abuse remains a continuing problem of great importance, many psychological disorders formerly resistant to drug treatment are increasingly the targets of drug therapy. Such disorders include bipolar illness, anxiety, panic disorder, phobias, and obsessive-compulsive disorder.

In the first edition of this text, the primary goal was to provide pharmacological information that was concise, accurate, and timely. The discussion was presented in clear language, as free of technical jargon as was possible, so that it could be easily understood by students and general readers with minimal background in the biological sciences.

This philosophy continues in this 20th anniversary edition. Yet recent research has dictated major content changes:

- Added to the detailed discussion of the drugs of abuse are new discussions of the anabolic-androgenic hormones, inhalants of abuse, and free-based methamphetamine (ICE).
- The many new psychotherapeutic agents are presented, along with their uses in treating bipolar illness, anxiety, panic disorder, specific and social phobias, and obsessive- compulsive disorder.
- The recent research in molecular biology of drug receptors has allowed new and much more sophisticated discussion of the receptors on which psychoactive drugs act. Although such presentation is technical, I think that its inclusion greatly demystifies drug action. Indeed, it allows the reader to visualize the receptors on which drugs act, and it provides introductory insights into how the process of receptor occupancy by a drug is translated into alterations in the intracellular chemistry of a neuron (the so-called process of signal transduction by intracellular second-messenger enzymes).
- The pharmacological intervention and treatment of psychological disorders that formerly were not amenable to drug therapy necessitate discussion of the interface between psychopharmacotherapy and the various professions of counseling, psychology, and psychotherapy. Those entering these and related professions now must be knowledge-

able about and conversant in the pharmacology of the drugs their clients or patients may be taking. To this end, each chapter contains brief discussion of this interface, and a new chapter, cowritten by a clinical psychologist, is totally devoted to this topic.

Features of the Seventh Edition

In its first two decades of publication, *A Primer of Drug Action* helped shape courses in psychopharmacology, drug abuse, and drug education. As it enters its third decade of publication, I have again completely revised and updated the book with the aim of continuing its history as the most current and most understandable drug education text available.

Two new chapters have been added to this edition (Chapter 9, "Drugs Used in the Treatment of Bipolar Disorder," and Chapter 16, "Psychology and Psychopharmacotherapy"). All other chapters have been extensively revised to update each topic of discussion. I have updated literature citations, and most are from 1993 and 1994. Included are discussions of both current and future directions in drug research (including new drugs that are, as of this date, on the horizon but not yet available for clinical use). The new material included in this edition includes

- New topics of drugs of abuse. These include the anabolic-androgenic steroids, inhalants of abuse, and ICE
- New focus on the mechanisms of drug-induced "reward" and how such mechanisms relate to a drug's potential for abuse
- Molecular biology of drug receptors, including

—the cannabinoid receptor and the endogenous neurotransmitter, anandamide

—the $GABA_A$ receptor and the action of benzodiazepines

—the presynaptic dopamine transporter and the action of cocaine

—the adenosine receptor and the action of caffeine

—the NMDA-glutamate receptor and the action of phencyclidine

—the presynaptic serotonin transporter and the action of antidepressants

—$GABA_A$ and $GABA_B$ receptor antagonists and partial agonists as cognitive enhancers.

—Serotonin$_2$ receptors and the action of psychedelic drugs

- New discussions on the treatments of mental disorders including bipolar illness, obsessive-compulsive disorder, panic disorder, and the anxieties

•New drugs, including

—*clozapine*
—*risperidone*
—*remoxipride*
—*venflaxatine and other serotonin-specific antidepressants*
—*flumazenil*
—*zolpidem*
—*buspirone*
—*carbamazepine, valproic acid, and other drugs for treating bipolar illness*
—*reversible MAO inhibitors*
—*Depo-Provera, Norplant, and mifepristone as contraceptives*

As in previous editions, I hope that this expanded and rewritten text will continue to serve the needs of all those who desire a concise, clearly presented introduction to the fields of psychopharmacology, drug education, and psychopharmacotherapy.

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Robert M. Julien, M.D., Ph.D.
November 1994

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CHAPTER 1

CLASSIFICATION OF PSYCHOACTIVE DRUGS

Psychoactive drugs are defined as substances that act to alter mood, thought processes, or behavior, or that are used to manage neuropsychological illness. Because the etiology of neuropsychological illness is often unknown and because the actions of drugs that are effective in treating such illness are complex, the classification of psychoactive drugs is not a straightforward task.

Several methods of classification have been formulated, but each has limitations. Certainly, an ideal method of classification would be based on a drug's mechanism of action. However, there is still too much that we don't know about those mechanisms to synthesize a comprehensive scheme.

Another possible classification scheme is based on the chemical structures of drugs; in this approach, it is assumed that drugs with similar chemical structures have similar effects. However, too many drugs with similar structures induce different pharmacological activity, and too many drugs with dissimilar chemical structures induce pharmacological activity that is nearly identical. Thus, the chemical structure of a drug does not produce a reliable guide to its pharmacological effects.

Perhaps the most useful classification of drugs is based on their most characteristic behavioral effects or the widest clinical use. A classification of drugs using these criteria is presented in Table 1.1.

TABLE 1.1 Classification of drugs and representative agents.

I. Traditional, nonselective CNS depressants
   A. Barbiturates: phenobarbital (Luminal), amobarbital (Amytal), pentobarbital (Nembutal), thiopental (Pentothal)
   B. Nonbarbiturate, nonbenzodiazepine hypnotics: meprobamate (Equanil), glutethimide (Doriden), methyprylon (Noludar), methaqualone, chloral hydrate
   C. Ethyl alcohol
   D. General anesthetics
   E. Inhalants of abuse

II. Antianxiety agents
   A. Benzodiazepines: diazepam (Valium), lorazepam (Ativan), triazolam (Halcion), others
   B. Nonbenzodiazepine, GABA-agonist hypnotic: zolpidem (Ambien)
   C. Nonbenzodiazepine, "second-generation" anxiolytic: buspirone (BuSpar)

III. Antiepileptic drugs
   A. Traditional agents: phenytoin (Dilantin), primidone (Mysoline)
   B. Benzodiazepines: clonazepam (Clonopin), clorazepate (Tranxene)
   C. Newer agents used in treating psychological disorders: carbamazepine (Tegretol), valproic acid (Depakene), alprazolam (Xanax)
   D. Newer meprobamate derivative: felbamate (Felbatol)

IV. Psychomotor stimulants (psychostimulants)
   A. Dopamine reuptake blocker: cocaine
   B. Dopamine-releasing agents
      1. Amphetamines: *d*-amphetamine (Dexedrine), methamphetamine
      2. Amphetamine derivatives: methylphenidate (Ritalin), pemoline (Cylert)
   C. Adenosine receptor blocker: caffeine
   D. Acetylcholine receptor stimulant (agonist): nicotine

V. Antidepressants
   A. Tricyclic antidepressants (TCAs): imipramine (Tofranil), amitriptyline (Elavil), others

Assumptions about Classification

There are several caveats to the classification scheme used in Table 1.1. First, the action of psychoactive drugs is not usually restricted to any one functional or anatomical subdivision of the brain. There are exceptions, of course (such as the use of levodopa for treating Parkinson's disease), but a psychoactive drug usually affects several parts of the brain simultaneously. This factor complicates the classification of drugs, because different behavioral effects may predominate at different doses. Some compromises must therefore be made.

TABLE 1.1 Classification of drugs and representative agents *(continued)*.

- B. Second-generation antidepressants: maprotiline (Ludiomil), amoxapine (Asendin), trazodone (Desyrel), bupropion (Wellbutrin)
- C. Serotonin-specific reuptake inhibitors: fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), clomipramine (Anafranil), venlafaxine (Effexor)
- D. Monoamine oxidase (MAO) inhibitors: tranylcypromine (Parnate), phenelzine (Nardil), isocarboxazid (Marplan)

VI. Mood stabilizers
- A. Lithium
- B. Carbamazepine (Tegretol)
- C. Valproic acid (Depakene)
- D. Adjunctive, nonspecific antimanic drugs
  1. Benzodiazepines: clonazepam (Klonopin), lorazepam (Ativan)
  2. Calcium-channel-blocking agents: Verapamil (Calan), nimodipine
  3. Clonidine (Catapres)

VII. Narcotic analgesics: opioids
- A. Pure opioid agonists (e.g., morphine, codeine, heroin)
- B. Partial opioid agonists (e.g., nalbuphine, pentazocine)
- C. Opioid antagonists (e.g., naloxone, naltrexone)

VIII. Antipsychotic agents
- A. Phenothiazines: chlorpromazine (Thorazine)
- B. Butyrophenones: haloperidol (Haldol)

IX. Psychedelics and hallucinogens
- A. Anticholinergic psychedelics: scopolamine
- B. Norepinephrine psychedelics: mescaline, DOM (STP), MDA, MMDA, TMA, DMA, Myristin
- C. Serotonin psychedelics: lysergic acid diethylamide (LSD); dimethyltryptamine (DMT); psilocybin, psilocin, bufotenine; ololiuqui (morning glory seeds); harmine
- D. Psychedelic anesthetics: phencyclidine (Sernyl), ketamine (Ketalar)
- E. Tetrahydrocannabinol: marijuana, hashish, cannabis

This table classifies drugs that alter mood or behavior, are useful in treating neuropsychological disorders, or are subject to compulsive abuse.

Second, the ultimate action of any given psychoactive drug may be explained by its effects on a specific neurotransmitter chemical. (The neurochemical processes that mediate transmission of information between neurons are discussed at some length in Appendix III.) Further, the same neurotransmitter chemical may be involved in many different activities of the brain (norepinephrine, for example, may be involved in temperature regulation, behavioral arousal, satiety, or rage). Thus, although a psychoactive drug might ultimately exert a single

effect on a specific neurotransmitter chemical, a variety of behavioral effects might follow if the neurotransmitter is involved in many different functions.

Third, it is important to understand that psychoactive drugs do not create new behavioral or physiological responses; they simply modify ongoing processes. The current view is that the behavioral effects induced by psychoactive drugs are secondary to their effects on biochemical and physiological processes, particularly those processes involved in the synaptic transmission in the brain.

Fourth, the classification of psychoactive drugs listed in Table 1.1 is not rigid. As noted, drugs ingested at different doses provoke different behavioral responses. Alcohol, for example, is classified as a general nonselective depressant despite the fact that, at low doses, it may cause behavioral excitation. Thus, classification alone does not clearly describe the pharmacology of a drug. It does, however, serve as a starting point for comparing compounds.

Fifth, certain factors that predispose persons to compulsive misuse of a drug must be considered when classifying centrally acting drugs. Such factors include physiological and psychological dependence and tolerance. Psychoactive drugs differ in their potential to induce such hazards. Clearly, any drug that can favorably alter a person's mood or behavior can induce psychological dependence—that is, a compulsion to use the drug for a favorable effect.

Further Discussion

In subsequent chapters, we describe specific agents within each class of psychoactive agents listed in Table 1.1. Alcohol and marijuana are discussed separately (in Chapters 5 and 13, respectively). Although both agents could be included in the chapter on sedative-hypnotic compounds (Chapter 3), they deserve separate discussions because of their wide range of use, ready availability, and social and legal implications. Similarly, the benzodiazepine and other more modern anxiolytic (antianxiety) compounds deserve their own discussion (Chapter 4), although their behavioral effects superficially resemble those of the barbiturates.

Chapter 8 discusses the antidepressant compounds, including those compounds likely to become available in the future. Chapter 9 presents a discussion of the mood stabilizers, which are compounds used to treat bipolar disorder (manic-depressive illness). The antidepressants (and lithium) have become widely used, and their unique properties clearly separate them from the psychomotor stimulants (Chapter 6).

Chapter 14 discusses drugs (in particular, oral contraceptives, fertility agents, and anabolic steroids) affecting the body hormones that influence the brain and behavior. Although these compounds are not psychoactive drugs, the wide interest in these drugs warrants the inclusion of this material.

Finally, Chapter 15 addresses the sociological issues of drug abuse, dependence, and addiction. Chapter 16 discusses individuals who are specifically involved in (or who are studying) the clinical interface between pharmacology and human neurophysiological dysfunction, bringing together the pharmacological and the nonpharmacological treatments of individuals with neuropsychological illness.

Before we discuss the individual classes of psychoactive drugs, however, we first look at the basic principles of drug action. This discussion (Chapter 2) lays the foundation for our later descriptions of psychoactive drugs.

CHAPTER 2

PRINCIPLES OF DRUG ACTION

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

This familiar scenario reveals the primary events of pain relief. The first is the *administration and absorption* of the drug into the body; the second is the *distribution* of the drug throughout the body; the third is the *interaction* of the drug with its "receptors" in the body, which are responsible for the drug's actions; and the fourth is the *elimination* of the drug from the body.

Pharmacodynamics, the study of these drug–receptor interactions, will be discussed later in this chapter. First, however, we will discuss *pharmacokinetics,* the study of how drugs move through and affect the body.[1]

PHARMACOKINETICS: HOW DRUGS MOVE THROUGH THE BODY

Pharmacokinetics, in its simplest form, describes the time course of a particular drug's actions—the time to onset and the duration of a drug's effects. Usually the time course simply reflects the amount of time required for the rise and fall of the drug's concentration at the target site. Simple though this may sound, the process of transporting a

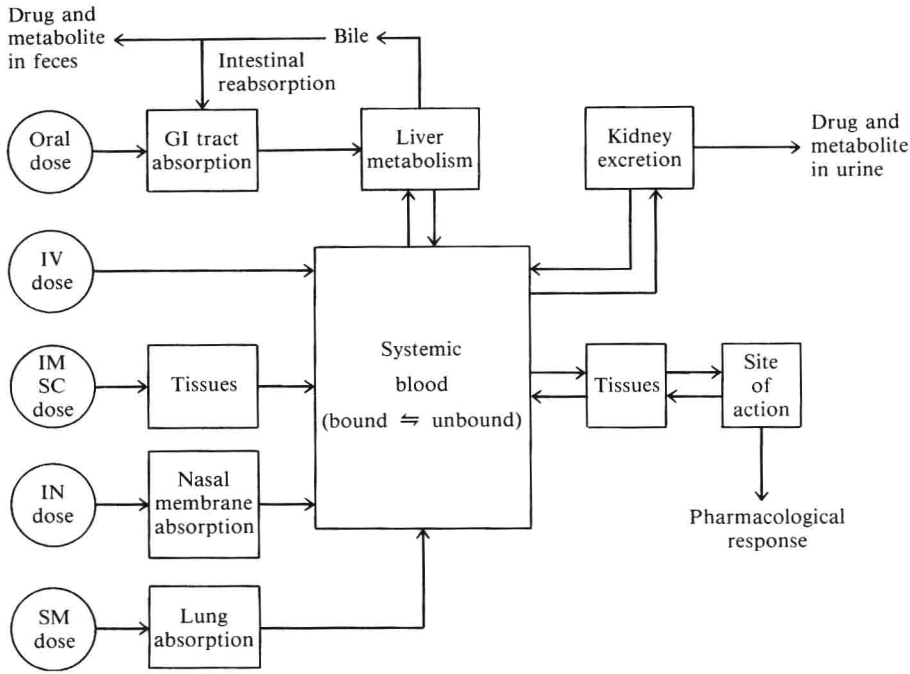

FIGURE 2.1 Schematic representation of the fate of a drug in the body. IM = intramuscular; IV = intravenous; IN = intranasal; SC = subcutaneous; SM = smoked. [Adapted from C. N. Chiang and R. L. Hawks, "Implications of Drug Levels in Body Fluids: Basic Concepts," in R. L. Hawks and C. N. Chiang, eds., *Urine Testing for Drugs of Abuse,* NIDA Research Monograph No. 73 (Rockville, Md.: National Institute on Drug Abuse, 1986), p. 63.]

drug from outside the body to its ultimate site of action inside the body is complex; a detailed picture of the process is given in Figure 2.1. Below we will briefly described the processes.

Drug Absorption

The phrase *drug absorption* refers to mechanisms by which drugs pass from the point of entry into the bloodstream. When administering any drug, one must select a *route* of administration, a *dose* of the drug, and a *dosage form* (liquid, tablet, capsule, or injection) 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.

Drugs are most commonly administered in one of five ways: orally (through the mouth), rectally (into the rectum), parenterally (by