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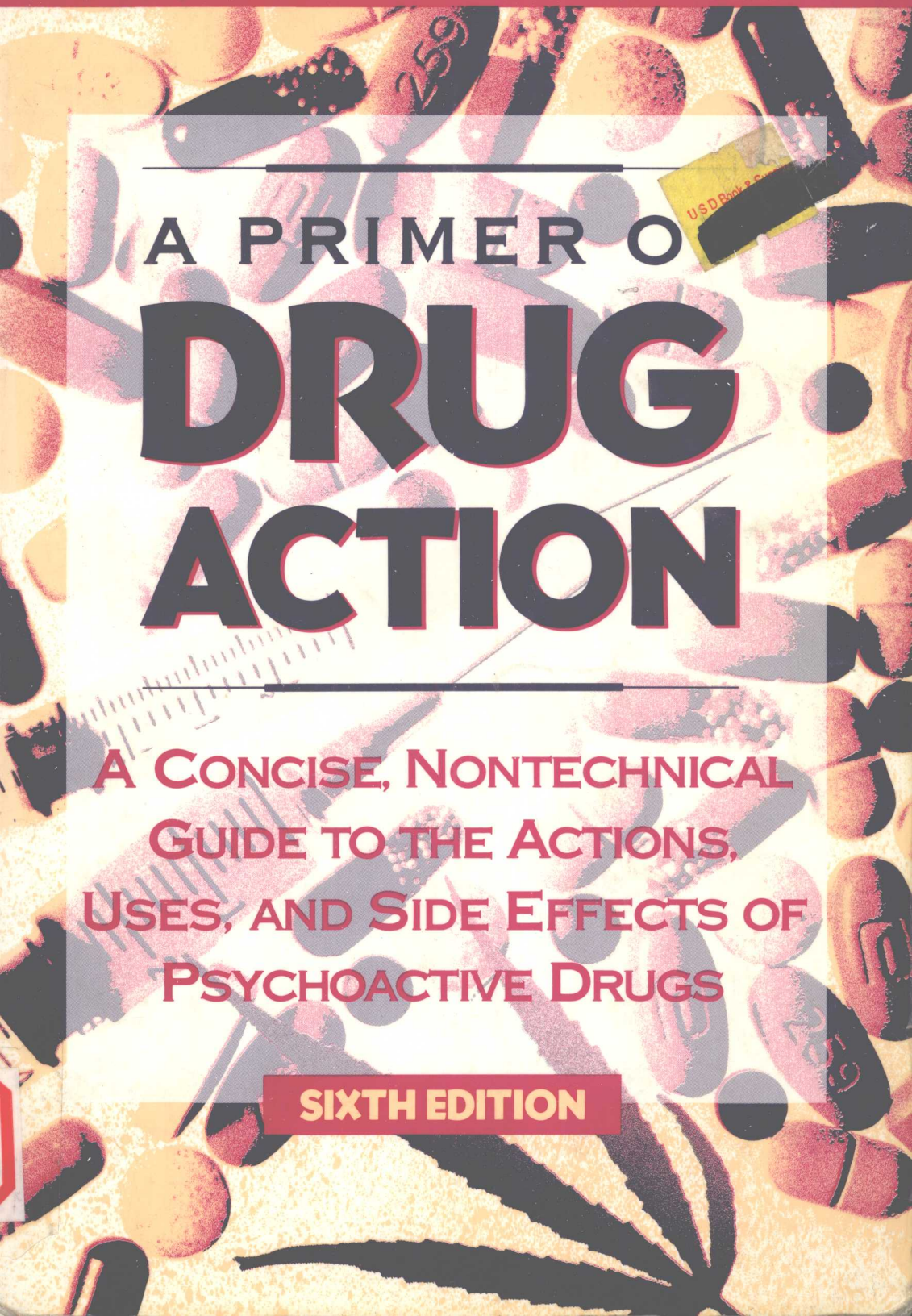

A PRIMER OF DRUG ACTION

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

SIXTH EDITION

A Primer of Drug Action

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

Sixth Edition

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To my wife, Judi,
for her understanding and support

Preface

In this age of science and discovery, it seems strange that many of us know very little about our own bodies, especially about the responses of our bodies to drugs. Perhaps this is because we take drugs so casually, but perhaps it is also because those who are not trained in medical or biological science have neither sought nor received information about drugs that is scientifically correct yet comprehensive and relevant to their lives. The purpose of *A Primer of Drug Action* is to provide readers with concise, accurate, and timely information about psychoactive drugs, that is, those drugs that exert their primary effect on the brain, thus altering mood or behavior, or that are used in the treatment of mental disorders.

My overall premise is that psychoactive drugs all act in predictable fashions, understood by examining their mechanisms of action. Each drug has inherent benefits, uses, risks, side effects, toxicities, and societal consequences. My objective has been to describe this information about drugs in clear language, as free of technical jargon as possible, so that it can be easily understood by students and general readers with little background in the biological sciences.

Since 1975, when the first edition of *A Primer of Drug Action* was published, vast amounts of new information have become available about both the actions of these drugs and the brain processes underlying neuropsychological function. Accompanying this growth of knowledge have been frequent updates of this text, culminating now in this sixth edition. This latest edition reflects the most recent developments and describes in new detail the mechanisms of action of psychoactive drugs; their pharmacological effects, uses, limitations, and toxicities; and the current state of knowledge of the brain mechanisms involved in mental illness or dysfunction.

Public awareness of drug risks and toxicities has markedly increased during the last two decades. This awareness is evidenced by the proliferation of rehabilitation and treatment programs, the recognition of drug dependence as a medical problem, the willingness of insurance programs to pay for rehabilitation, the increased enforcement of drug laws, and the growing public intolerance of cigarette smoking, driving by alcohol-intoxicated persons, and other drug use.

Despite this increased awareness, there is much about drug use that is still distressing: every year, more than 450,000 people still fall victim to cigarette toxicities, alcohol burdens the lives of millions of people, cocaine use is seriously damaging an increasing number of users as well as their offspring, marijuana has become a part of our culture, experimentation with various psychedelic drugs continues, and drug use by minors continues to be a problem. Hence, the emphasis of *A Primer of Drug Action* remains focused on those drugs that primarily affect human thought and behavior as well as on the broader field of neuropsychopharmacology. This text can also be coupled with my companion text, *Drugs and the Body* (New York: W. H. Freeman and Company, 1988), to provide a comprehensive introduction to the wider science of pharmacology.

Features of the Sixth Edition

A Primer of Drug Action has become a classic text for courses in psychopharmacology and drug education. Now, in this sixth edition, I have completely revised and updated the entire book with the aim of making it the most current and understandable drug education text for the 1990s.

Two new chapters have been added to this edition (Chapter 5, "Benzodiazepines," and Chapter 7, "Caffeine and Nicotine"). These topics were included in earlier editions, but they are now given ex-

panded discussion and emphasis. All other chapters have been revised to update and clarify the presentation of pharmacology, drug mechanisms, and the physiological basis of psychological disorders. In addition, I have reorganized the presentation to more clearly separate pharmacokinetics (how the body handles drugs) and pharmacodynamics (how drugs affect the body, including their mechanisms of action). References have been updated throughout; indeed, most are from the years 1989 and 1990. I have included 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), and I have added study questions at the end of each chapter. Much new material is included:

- The mechanisms of action of both psychoactive drugs and those drugs used in the treatment of neuropsychological illness
- The toxicities associated with the use and abuse of alcohol, cigarettes, caffeine, opioids, marijuana, oral contraceptives, and phencyclidine
- Psychoactive drugs as behavioral reinforcers and the role of such action in drug dependence
- The effects of psychoactive drugs on the fetus
- The neurochemical basis of anxiety and panic disorders, excessive alcohol ingestion, manic-depressive affective disorders, schizophrenia, dementia, attention-deficit hyperactivity disorder, parkinsonism, and both central and peripheral components of pain and analgesia
- New drugs, including
  - serotonin-reuptake blocking antidepressants
  - benzodiazepine antagonist
  - atypical antidepressants
  - selective MAO-A inhibitors
  - newer opioid analgesics
  - atypical antipsychotics
  - new drugs for parkinsonism
  - injectable analgesic–anti-inflammatory agents
  - implantable female contraceptives
  - injections for male contraception
  - abortifacient

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 field of neuropsychopharmacology.

Robert M. Julien
June 1991

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CHAPTER 1

Principles of Drug Action

HOW DRUGS ARE HANDLED BY THE BODY: PHARMACOKINETICS

A drug must be present in the body and in an adequate concentration (or amount) for it to act at its target site—the specific site in the body where it can exert its effect. Usually the time course of a particular drug's action simply reflects the amount of time required for the rise and fall of its concentration at the target site. Thus, most drugs that are ingested must somehow get from the external world into the bloodstream and, ultimately, to their target sites, where they can exert their effects. (A few drugs, which are classified as topical drugs, act on the skin, genitalia, or gastrointestinal tract; they do not actually enter the body. Topical drugs are not discussed in this text.)

Simple though this may sound, the process of transporting a drug from outside the body to its ultimate site of action is very complex. The action of any drug (that is taken by any means other than intravenous injection) depends on the *absorption* of that drug into the bloodstream, the *distribution* of the drug by the circulating blood to all regions of the

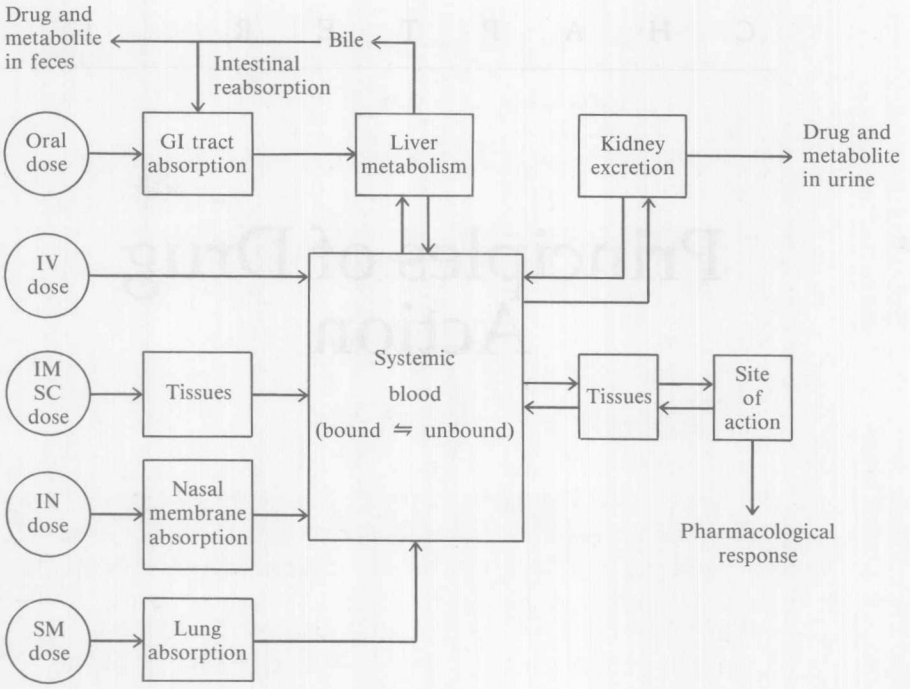

FIGURE 1.1

Schematic representation of the fate of a drug in the body. IV = intravenous; IN = intranasal; 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.]

body, the tissue action of the drug itself, the eventual breakdown of the drug into an inactive compound, and, finally, the excretion of the drug (Figure 1.1). *Pharmacokinetics* is the term applied to that area of pharmacology in which the factors that influence the absorption, distribution, metabolism, and excretion of drugs are elucidated.[1,2] Thus, let us consider briefly the processes that are involved.

Drug Absorption

The term *drug absorption* refers to those mechanisms by which non-injected drugs pass from the point of entry into the bloodstream. When administering any drug, one must be able to select a *route* of administra-

tion, a *dose* of the drug, and a *dosage form* (liquid, tablet, capsule, or injection) that will place the drug at its site of action in a pharmacologically effective concentration and maintain that 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 injection), by *inhalation* through the lungs, and by *absorption* through mucous membranes. Let us consider these methods of administration and absorption in more detail.

Oral Administration

Drugs are most commonly taken by mouth and swallowed. To be effective when administered orally, the drug must be soluble and stable in stomach fluid, be carried to the intestine, penetrate the lining of the intestine, and pass into the bloodstream. Indeed, the amount of drug that can be absorbed depends on its solubility (in stomach fluid) and permeability (through the lining of the intestine).

Because they are already in solution, drugs that are administered in liquid form tend to be absorbed more rapidly than those given in tablet or capsule form. Alcohol, for example, is taken in liquid form. As a result, about one-fourth to one-third of the alcohol that is ingested is absorbed directly from the stomach into the bloodstream. Thus, absorption is rapid and the effects of the alcohol may be felt very rapidly, especially if no food contents are present in the stomach. When a drug is taken in solid form, the rate at which it dissolves will limit its rate of absorption.

After a drug dissolves in the stomach, its subsequent absorption into the bloodstream begins with the passive transfer of that drug across the stomach or intestinal lining. This process occurs against a developing concentration gradient of drug at a rate that is determined by the ratio of water solubility to lipid solubility of the drug molecules. Indeed, once they are in in the body, drugs exist as a mixture of two interconvertible forms: one that is water-soluble (the ionized, or electrically charged, form) and one that is lipid soluble (the un-ionized, or uncharged, form). When the drug molecule is in the water-soluble form, it does not readily cross lipid membranes; in the lipid-soluble form, it can freely permeate the membrane.

The extent to which a drug is present in each form depends on the relative acidity (pH) of the fluid in which it is dissolved and on a characteristic of the drug molecule itself (its pK_a—the pH at which 50

percent of the drug is ionized).* Gastric juice is very acidic; intestinal contents are less acidic; and plasma (the noncellular component of blood) is slightly alkaline. As we have already stated, only lipid-soluble molecules diffuse readily across cell membranes—the level of lipid-soluble drug is the limiting factor that determines the passage of a drug across a lipid membrane.

If the pH is different on the two sides of a membrane (as, for example, between the stomach and the bloodstream), the ratio of water-soluble drug to lipid-soluble drug will also be different on the two sides of the membrane. At equilibrium, the concentration of the lipid-soluble drug will be equal on both sides of the membrane (because, as we have said, the lipid soluble form of the drug can freely permeate the membrane); but the *total* quantity of drug will be higher on the side where the ratio of water-soluble drug to lipid-soluble drug is greater (because the water-soluble drug molecules are unable to traverse the membrane). Thus, a drug is *absorbed* against its concentration gradient by passive transfer, without expenditure of the energy that would be necessary to maintain an active (energy-requiring) pump to move molecules against a concentration gradient.

Although oral administration of drugs is common, it does have disadvantages. First, it may lead to occasional 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 predicted accurately because of unexplained differences between individuals and differences in the manufacturing of drugs. (Indeed, different brands of the same drug may be absorbed at widely differing rates.) Third, some drugs, such as the local anesthetics (Chapter 13) and insulin, when administered orally, are destroyed by the acid in the stomach before they are absorbed. To be effective, such drugs must be administered by injection.

Despite the disadvantages, in general, about 75 percent of an orally-administered drug will be absorbed by the body within about 1 to 3

*The ratio of lipid-soluble (un-ionized) drug to water-soluble (ionized) drug at each pH (and, therefore, in each body compartment) can be calculated from the Henderson-Hasselbalch equation:

$$pH = pK_a + \log\left(\frac{\text{base}}{\text{acid}}\right)$$

For drugs that are weak acids, the *acid* form of the drug is the un-ionized form; for drugs that are weak bases, the *base* form is un-ionized. The reader who is interested in a more in-depth discussion of this chemistry is referred to any of the several textbooks of pharmacology listed in the bibliography.