SECOND EDITION

DRUGS AND HUMAN BEHAVIOR

DAVID M. GRILLY

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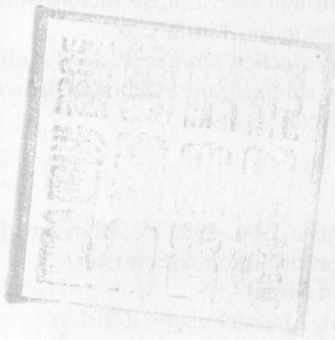

Allyn and Bacon

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A Division of Simon & Schuster
160 Gould Street
Needham, Massachusetts 02194

Library of Congress Cataloging-in-Publication Data

Grilly, David M., 1944–
Drugs and human behavior / David M. Grilly. —2nd ed.
p. cm.
Includes bibliographical references and index.
ISBN 0–205–15361–5
1. Psychopharmacology—Popular works. I. Title.
RM315.G75 1994
615'.78—dc20 93–17310
CIP

Printed in the United States of America
10 9 8 7 6 5 4 3 2 97 96 95 94

Preface

It is a very rare person who does not, at some time or another, use a psychoactive drug—that is, a drug that alters psychological processes such as mood, thought, and behavior. In fact, some drugs, such as caffeine, nicotine, and alcohol, are so common in our society that we usually do not even think of them as drugs. Although the use of psychoactive drugs has a long history, the actual systematic study of the relationships between drugs and psychological processes—psychopharmacology—is quite new. Therefore, our knowledge about psychoactive drugs is relatively limited. This is rather unfortunate because their use is pervasive in most Western cultures, particularly our own. Drugs are used in a wide variety of social, recreational, and therapeutic settings.

The purpose of this book is to introduce the student to the field of psychopharmacology, with special emphasis on the relationships between drugs, their mechanisms of action in the nervous system, and human behavior. For most students this book will be their first exposure to this diverse field. The text is written for the psychology student who wishes to go into some field of research associated with drugs or into clinical areas where the persons they deal with are taking psychoactive medications or using psychoactive drugs recreationally, and perhaps abusing them. It is also written for nursing students, who will be observing patients who are prescribed psychoactive medication; chemistry students, who may be interested in going into pharmacy; biology students, who may enter the field of medicine and eventually prescribe a number of psychoactive medications for their patients; and any other students interested in the fascinating relationships among drugs, the brain, emotions, mental activities, and behavior.

Because psychopharmacology involves biological functions, chemical reactions, physics, and psychological processes, ideally students reading this book will already have a basic familiarity with each of these areas. The text is not written for the specialist. Therefore, the use of esoteric and specialized jargon to describe the effects of drugs and the psychiatric and psychological conditions they induce or alleviate has been minimized. Key pharmacological terms are set in boldface type and defined the first time they appear. Other scientific and clinical terms which could impede the student's understanding of certain principles are italicized and defined. All definitions in this text are from the following sources: *Stedman's Medical Dictionary*, 25th Edition; *Dictionary of Psychology* by A. S. Reber; *Mosby's Medical and Nursing Dictionary;* and *Webster's Deluxe Unabridged Dictionary*, 2nd Edition.

It is hoped that the information contained in this book will enable the student to appreciate more fully why people use drugs and what the consequences of that use might be. Chapter 1 deals briefly with the field of psy-

chopharmacology from a historical perspective. Chapters 2 and 3 acquaint the student with the principles and mechanisms behind the actions of drugs that can be generalized to all drugs, including those affecting mood, mental functions, and behavior. Chapters 4 and 5 review the nervous system, through which psychoactive drugs induce their effects. All thoughts, emotions, and behaviors are the result of electrical and biochemical activities taking place in the nervous system, and drugs that affect these psychological variables do so by disturbing or altering these activities. Without an understanding of the basic mechanisms behind these electrical and biochemical events, it will be very difficult for the student to appreciate and understand why psychoactive drugs do what they do. These first five chapters contain definitions of psychopharmacological terms and describe concepts necessary for understanding the processes and actions of the drugs to be discussed in the remaining chapters.

Chapter 6 discusses the general processes behind drug tolerance, drug abuse, and drug dependence. Chapters 7 through 11 classify, describe, and discuss the actions and effects of drugs commonly used in our culture for social and recreational purposes, often leading to drug abuse and dependence. Many of these drugs have been or still are being used in a medical or psychiatric context, but their present impact on our society is due primarily to their use in nonmedical settings. These are the drugs with which the students themselves may have direct contact.

Chapters 12 through 14 describe and discuss the actions and effects of drugs used primarily in the treatment of medical and emotional disturbances. Although these drugs are used in a medical context, many students in psychology, biology, chemistry, and nursing will go on to specialize in clinical fields where the patient population has been prescribed such medications. In order to deal fully with the needs of their clients, these clinicians should be aware of what these drugs are capable of doing, what their side effects are, and why they are being prescribed. Even students who do not become clinicians should be aware of these properties because there is a strong likelihood that they will have friends or families who do use these drugs.

I would like to thank the many students I have taught over the years who have provided the inspiration behind this book and whose comments and suggestions on the first edition led to considerable modification in the organization of the second edition. I am most indebted to Barb Simon for her assistance in putting this second edition together and making it more readable from the standpoint of the student. Finally, I would like to thank the reviewers—Helen M. Murphy, Ph.D., John Carroll University; Dr. Mark Masaki, Youngstown State University; Robert W. Bell, Ph.D., Texas Tech University; and John Broida, Ph.D., University of Southern Maine—and also my colleagues, listed here, who read and commented on the manuscript at various stages. Their comments were invaluable. They include Gaylord Ellison, University of California, Los Angeles; Dennis Glanzman, Arizona State University; Carol van Hartesveldt, University of Florida, Gainesville; Keith Jacobs, Loyola University, New Orleans; Frank White, Neuropsychopharmacology Laboratory, Lafayette Clinic; W. Jeffrey Wilson, Purdue University at Fort Wayne.

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Chapter One

Psychopharmacology in Perspective

Psychopharmacology is the systematic study of the effects of drugs on behavior, cognitive functioning, and emotions. Drugs that alter behavior, cognitive functioning, or emotions are called **psychoactive** or **psychotropic drugs**. The term "psychopharmacology" is a combination of the terms "psychology" and "pharmacology," which refer, respectively, to the study of the variables affecting behavior and the study of the effects of drugs on biological systems. Originally "psyche" referred to the soul, but lately it has been used to refer to the mind. "Pharmakos" originally meant scapegoat; a pharmakos was a person who was sacrificed as a remedy for whatever maladies another person might have been experiencing. For obvious reasons, there were few volunteers for the position, but I suppose that the procedure worked in roughly a third of the cases—about the same success rate one might get nowadays using a placebo. Later on, around 600 B.C., the term came to refer to a medicine, drug, or poison. Presently, the term "drug" is used in a much more general way to denote chemicals that alter the normal biological functions of the body.

Psychoactive drugs are chemicals that induce psychological effects by altering the normal biochemical reactions that take place in the nervous system. A drug's chemical structure, how much of the drug is taken, how long it has been since it was taken, and how frequently it is taken are important factors that will be discussed in relation to the drug experience. In addition, three other ingredients in the drug experience should always be kept in mind: the **set** (the psychological makeup and the expectations of the individual taking the drug), the **setting** (the social and physical environment in which the drug is taken), and the individual's unique biochemical makeup (Wallace & Fisher, 1991). Factors such as the physical setting and the person's body chemistry, attitudes, emotional state, and previous drug experiences all interact with the drug to

alter the person's level of awareness, mood, thought processes, and behavior. When one attempts to describe the effects of a particular psychoactive drug, these factors should always be taken into consideration.

A drug should not be viewed as simply bad or good. Consideration must be given to how much is taken, what it is taken for, and in what context it is taken. For example, heroin can be a very effective drug in the treatment of pain in terminally ill cancer patients, and cocaine is a very effective local anesthetic for use in certain kinds of surgery. However, when injected in unknown quantities for their euphoric properties, these drugs can lead to dependence, economic and social disaster, incarceration, toxic reactions, and death.

A Historical Overview of Psychopharmacology

Ancient records indicate that human beings have been using drugs to alter mood and behavior for a long time. (For fascinating and more detailed versions of this topic, see Brecher, 1972; Caldwell, 1978; and Szasz, 1974.) Considering the thousands of plants available that contain psychoactive substances and the likelihood that our ancestors were just as curious and willing to experiment on themselves as some people are today, this information should not come as any surprise. Substances that can induce mystical experiences and hallucinations are found in cannabis and in numerous herbs, mushrooms, and cacti, all of which grow throughout the world.

In order to enhance their ferociousness, early Viking warriors were said to ingest the mushroom *Amanita muscaria*, which is capable of inducing gaiety, exuberance, and berserk behavior—a term derived from their name, the Berserkers. Some American Indians have used the peyote cactus, which contains the hallucinogen (hallucination-producing substance) mescaline, in their religious ceremonies for centuries. Archaeological findings of "mushroom stones" in Guatemala indicate that a sophisticated mushroom cult existed there some 3,500 years ago. Early Spanish chroniclers wrote of their opposition to the Aztecs' ceremonial eating of the diabolical mushroom *teonanacatl* (food of the gods) for purposes of divination, prophecy, and worship. It is likely that these mushrooms contained the hallucinogenic substances psilocybin and psilocin. Cannabis, which we now call marijuana, was first used more than 4,000 years ago, primarily for its medical value in treating a number of different ailments.

Opium poppies, which contain the narcotics morphine and codeine, were probably used by the ancient Sumerians in Mesopotamia almost 7,000 years ago. Substances that effectively suppress manic symptoms can be found in rauwolfia, a plant common to the Himalayas. Substances

that elevate mood and reduce fatigue are found in many plants. For centuries South American Indians have chewed the coca leaf, which contains small amounts of the drug cocaine, to alleviate fatigue, elevate mood, and reduce hunger, and archaeological evidence suggests that early humans may have used coca as far back as 3000 B.C.

The use of tea as a pleasurable stimulant began about A.D. 600 in China. An intoxicating beverage made from coffee beans was introduced to the Arabians in the 13th century. Numerous other plants containing caffeine or similar-acting substances have been used by ancient cultures in Mexico, South America, and Africa, among many others. The use of nicotine-containing tobacco by both South and North American Indians goes back at least 600 years.

In ceremonies during medieval times, witches used various herbs (such as mandrake, henbane, and belladonna) containing scopolamine, hyoscyamine, and atropine to induce hallucinations and the sensation of flying. They also may have thrown in a few toads, whose sweat glands contain the hallucinogenic drug bufotenine, one of the few psychoactive drugs of animal origin. Physicians during this and later periods used the same substances as sleep inducers and analgesics, as well as for other purposes.

Except perhaps for caffeine, the most common psychoactive substance used around the world today is alcohol, and it has been available for thousands of years. There is hardly a culture, primitive or advanced, that does not value its peculiar properties. Alcohol is a simple product of fermentation, which occurs when certain yeasts, molds, and bacteria act upon sugar in a variety of fruits and which is easily produced both accidentally and purposefully. The earliest records of purposeful alcohol production were made by the Egyptians more than 5,500 years ago.

Every culture that we are aware of has used a plant or plants with psychoactive properties at one time or another. In their experimentation over the centuries, human beings must have eaten, drunk, smoked, or rubbed on their bodies thousands of substances. They found that some of these substances nourished them, while others made them ill or killed them, relieved their psychological or physical discomforts, or had extraordinary and incomprehensible effects on mood, consciousness, or behavior.

Even nonhuman animals have been observed to seek out substances with mood-altering properties (Siegel, 1989). Elephants, chimpanzees, baboons, and horses have been noted to prefer water containing a small percentage of alcohol over pure water. Some birds prefer fermented berries over unfermented berries. Goats nibble coffee berries; some species of bees guzzle stupefying nectars of specialized flowers; llamas chew coca leaves (which contain cocaine); and some species of ants maintain "herds" of beetles, apparently for their intoxicating secretions.

These observations have led Siegel to propose the intriguing—and controversial—hypothesis that intoxication is a universal "fourth drive," as natural as the innate drives of hunger, thirst, and sex.

Predecessors to Modern Pharmacotherapies

During the 1800s a number of psychoactive drugs were isolated or distilled from plants or developed from nonplant sources. Morphine was isolated from opium in 1805 and was viewed as a most effective treatment for periodic insanity. Cocaine was extracted from the coca leaf in 1857 and was suggested as a potential treatment for depression. Bromine, discovered in 1826, and chloral, discovered in 1832, were used as sedatives and sleep-inducing agents. The anesthetic gases chloroform and nitrous oxide were suggested as potential treatments for insanity. Compounds such as cannabis, hemlock, strychnine, and *Datura stramonium*—used for centuries to treat a variety of disorders—were still viewed as valuable psychiatric tools, although we realize today that they probably did more harm than good. The first phenothiazine (a type of antipsychotic discussed in Chapter 12), methylene blue, was developed in 1883. A few years later, it was reported to have calming effects on manic and hallucinating patients. Despite its apparent effectiveness, it would take another 50 years before the closely related compound chlorpromazine would revolutionize the treatment of the severely mentally disturbed. Drug-induced sleep therapy, where emotionally disturbed patients were kept unconscious for several days, became popular toward the end of the 19th century.

It was during the 1800s that investigations of the formal relationships between drug variables and psychological processes, particularly those involved in mental illness, began. The first of these investigations was probably that conducted by Jacques-Joseph Moreau de Tours, a highly respected physician in France. In the mid-1800s he published a book, for which he is most noted, called *Hashish and Mental Illness.* After taking a hashish-laced concoction (hashish is a concentrated form of marijuana) on numerous occasions and observing others who volunteered to ingest his concoction, he compared the drug-induced symptoms with the mental symptoms that occur spontaneously in psychoses. Moreau was one of the first to emphasize that the person's particular or immediate context greatly influenced both the quality and intensity of the drug experience. He also observed the effects of hashish on some of his patients with mental disorders and suggested that hashish-induced excitement may be beneficial in treating depressed patients. He reported that some depressed individuals, after taking his hashish concoction, chatted, laughed, and acted silly all evening. Unfortunately, however, those effects were transitory, and the patients relapsed. He also found that occasionally manic patients improved after taking hashish.

Moreau also studied the psychoactive effects of opiates, nitrous oxide, and a number of sedative-hypnotic drugs. Unfortunately, his work in this area went largely unrecognized by his contemporaries, but shortly after *Hashish and Mental Illness* was published, a few American psychiatrists who read of his work tried cannabis preparations in the treatment of insanity. Despite the lack of recognition during his time, today some people view Moreau as the first psychopharmacologist.

However, the very first book in modern experimental psychopharmacology, as well as the first book solely devoted to drugs and animal behavior, was published in 1826 by A. P. Charvel, a young medical student (Siegel, 1989). Charvel studied the effects of opium on a variety of animals, including water beetles, crayfish, snails, fish, toads, birds, and various mammals (including himself and other medical students). Like Moreau, Charvel discovered that a drug's effects depend on numerous factors, such as the individual's past history, tolerance to the drug, dose, and method of administration. But like the observations of Moreau, Charvel's discoveries were largely ignored by his contemporaries.

During the late 1800s and early 1900s, some of psychology's most famous forefathers were also some of the first to explore systematically the relationship between various drugs and psychological variables. Early in his career, Sigmund Freud spent three years investigating the effects of cocaine on fatigue, depression, strength, and morphine addiction, among other things. In many of these studies, he was the test subject. Until recently, many of the most comprehensive, up-to-date descriptions of cocaine's effects were contained in Freud's 25-page essay "Über Coca" (On Coca) published in 1884. However, a growing number of reports critical of cocaine at that time, as well as Freud's own dismal failure in treating a good friend's morphine addiction with cocaine (the friend turned from morphine to heavy cocaine use), led him to direct his scientific interests into very different areas. However, Freud retained an interest in drugs and behavior throughout his lifetime. Curiously, although Freud was able to give up cocaine, apparently with very little discomfort, he remained a nicotine addict who chain-smoked cigars despite suffering from angina (chest pain) and having had multiple operations for oral cancer (Brecher, 1972). Even the man who discovered the ego-defense mechanism of "denial" was unable to avoid its consequences.

Ivan Pavlov, best known for his work in the conditioning of reflexes, attempted to treat schizophrenics by using some of his conditioning techniques and inducing long periods of sleep with bromides. However, it is doubtful that he was very successful with this technique, because bromides tend to accumulate in the body and can reach levels that can induce toxic symptoms such as headache, sedation, violent delirium, mental confusion, and gastric distress. In some cases, these symptoms are very similar to those of a psychosis. Pavlov's work in the area of conditioning reflexes led some of his colleagues to use drugs like

morphine as potential stimuli for the induction of new reflexes. These researchers probably did not realize just how important the Pavlovian process is in what we now refer to as drug dependence.

William James, the first American-born psychologist, wrote about some of his fascinating experiences while under the influence of nitrous oxide, sometimes known as "laughing gas" (Leavitt, 1982). He found that consciousness, in which he was very interested, could be profoundly altered by nitrous oxide, although not necessarily for the better. It seems that while he was under the influence of nitrous oxide (the effects last but a few minutes) he was capable of very mystic revelations. Unfortunately, though, he could never remember what the revelations were when the effects wore off. It is reported that upon one occasion while under the influence he was able to quickly jot down one of these profundities. It read:

> Hogamous, higamous
> Man is polygamous
> Higamous, hogamous
> Woman is monogamous (Gibbons & Connelly, 1970, p. 77).

The first half of the 20th century was accompanied by the synthesis or clinical use of a wide variety of new psychoactive substances with potential therapeutic value. Barbiturates were introduced in 1903 and helped sustain interest in sleep therapy for various mental ailments. Amphetamine, first synthesized in the 1800s, came into clinical use in 1927 in the treatment of narcolepsy and mild depressive states. Albert Hofmann first synthesized lysergic diethylamide (LSD) in 1938. Five years later, when he accidentally ingested LSD during one of his experiments, he discovered that it was one of the most potent psychoactive substances known to humankind. LSD would be used a few years later as a psychedelic (mind-manifesting) adjunct to psychotherapy and as a means of inducing what many people believed to be a model psychosis.

Despite the extensive history of drug use and these early investigations, there was no real interest in studying drugs and their influence on cognition, emotions, and behavior until about the early 1950s. During the 1950s a drug previously used in France as a preanesthetic was tested on some schizophrenic patients and was found to induce a dramatic reduction in their symptoms. Previously, many different drugs had been used in treating schizophrenia, all of which simply put the patients to sleep or made them so drowsy or sedated that they could not do anything. This particular drug, however, did more than simply calm the patients; it worked by reducing the core symptoms. The drug was known as chlorpromazine, and, as we will see shortly, it was this discovery that led to the formation of the formal and distinct discipline known as psychopharmacology.

One of the first antihistamines was developed in 1937. Although antihistamines were initially used in the treatment of allergies, their sedative properties, viewed by those taking them for allergic conditions as an undesirable side effect, were suspected as being beneficial in the treatment of other clinical conditions. The antihistamine promethazine was introduced in 1949 as an adjunct to surgery. It was found to reduce surgical shock, to calm patients both before and after major surgery, and to reduce the emotional suffering associated with surgery. A year later it was used by a psychiatrist in the treatment of schizophrenia, primarily for its hypnotic effects. Although promethazine calmed his patients, the psychiatrist apparently saw it as just another sedative. In the same year another psychiatrist noted similar calming effects in schizophrenic patients with a related compound, but the manufacturer was not interested in developing such a drug. However, reports of these effects in surgical patients and schizophrenics eventually led to the evaluation and development of compounds with similar structures with even more specific actions.

One of these compounds, initially called 4560 RP, was found to have some interesting pharmacological properties. It had minimal antihistaminic action, but it reduced both sympathetic and parasympathetic activity, abolished conditioned reflexes, and had a host of other desirable properties. In clinical trials it abolished preoperative anxiety, reduced surgical stress, and eliminated the postoperative consequences of stress. Here was a drug that could turn off the world and its harrowing stress without inebriating the patient or putting the patient to sleep. The surgeon who attempted these clinical tests closed his report with the suggestion that 4560 RP, now called chlorpromazine, be used in treating psychiatric conditions. The first report on chlorpromazine treatment of psychosis was published in France in 1952. In 1953 chlorpromazine was tried more extensively in psychiatric wards in Paris.

It could be said that at that time chlorpromazine started the pharmacological revolution in psychiatry. Although it did not cure mania and schizophrenia, chlorpromazine did suspend their symptoms with great efficacy and much less toxicity than any previous drug. Chlorpromazine was used immediately in Italy and Switzerland, and shortly thereafter in the United States. Its use spread to England and South America in 1954 and to Australia, Japan, and the Soviet Union in 1955. Its trade name in Europe was Largactil, because of its *larg*e spectrum of therapeutic *acti*vity. In the United States it was marketed as Thorazine, perhaps after the powerful god of thunder, Thor (although this derivation is purely speculative).

The pharmacological revolution expanded. Between 1952 and 1954, chlorpromazine monopolized drug therapy for all mental diseases. It stirred the ambitions of drug manufacturers and researchers. New drugs were developed, and drugs that had been abandoned were clinically

tested again. In India as early as 1931 it was suggested that the rauwolfia plant, which contains reserpine, had some beneficial effects in the treatment of mental disorders, but it was not introduced to the Western world until 1954. Meprobamate, the first of the so-called anxiolytics (anxiety reducers), was first used clinically in 1955 and became as popular for the treatment of neuroses as chlorpromazine was for psychoses. The treatment of depression with a monoamine oxidase inhibitor became acceptable in 1957, five years after its antidepressant action was noted in tuberculosis patients who were administered the drug for its antituberculosis properties. A drug developed in 1948, with properties that did not generate any enthusiasm on the part of its manufacturer, was again tested clinically in 1957 because of its molecular resemblance to chlorpromazine. Unlike the phenothiazines, however, the drug was relatively ineffective in quieting agitated psychotic patients. Instead, it seemed to have remarkable mood-lifting properties in severely depressed patients. Thus was born the first tricyclic antidepressant, imipramine (Tofranil).

The enthusiasm created by chlorpromazine led to one oversight with respect to a drug that would later take the place of chlorpromazine as one of the most valuable treatments for cyclical mood disorders. As early as 1870, it was suggested that, in one of its salt forms, lithium, an alkali metal, had mood-altering effects. It wasn't until 1949, however, that the Australian psychiatrist John Cade discovered, quite fortuitously, that lithium had profound mood-stabilizing effects in manic patients. Despite verification of his findings in studies conducted one or two years later, the vast majority of psychiatric practitioners remained unimpressed with his findings. Lithium was believed to be too toxic. It also had minimal marketability because it was unpatentable as a natural substance. In addition, chlorpromazine suppressed the symptoms of mania much more quickly than lithium did and had a much lower potential for toxicity. It took almost 10 years for the medical community, at least in the United States, to recognize the true value of lithium and to rectify the oversight.

Even LSD research advanced because of chlorpromazine and the interest stimulated between brain biochemistry and psychosis. Because chlorpromazine could readily block the effects of LSD, it made research and psychotherapy with LSD safer. LSD psychosis became the model with which other potential antipsychotic drugs could be tested, and with LSD inducing a model psychosis, it became a tool in exploring the etiology (the science of causes or origins of diseases) of schizophrenia. Unfortunately, we now know that the LSD psychosis is considerably different from the psychoses that occur "naturally" in humans.

Beginning in the early 1950s, a multitude of drugs were developed that revolutionized the treatment of major mental and emotional illnesses. Despite the increase in the general population, the number of