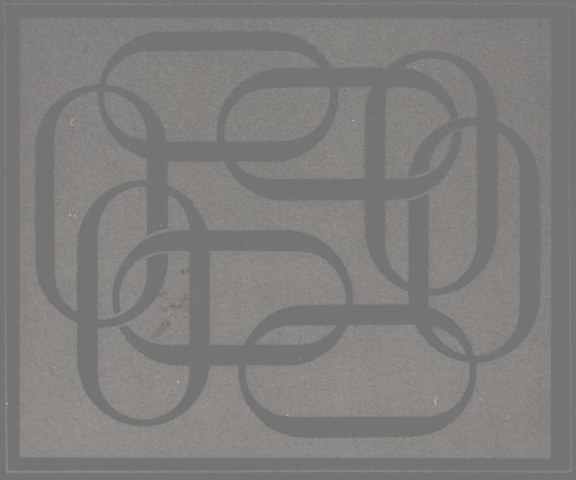
DRUGS AND BEHAVIOR



WILLIAM A. McKIM

AN INTRODUCTION TO BEHAVIORAL PHARMACOLOGY

DRUGS AND BEHAVIOR

An Introduction to Behavioral Pharmacology

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Library of Congress Cataloging-in-Publication Data

McKim, William A.,
Drugs and behavior.

Includes bibliographies and index.
1. Psychopharmacology. 2. Psychotropic drugs.
I. Title. [DNLM: 1. Behavior—drug effects.
2. Psychopharmacology. 3. Psychotropic drugs.
QV 77 M158d]
RM315.M36 1986 615'.78 85-16756
ISBN 0-13-220732-X

Editorial/production supervision and
interior design: Debbie Ford
Cover design: Ben Santora
Manufacturing buyer: Barbara Kelly Kittle

Printed in the United States of America

10 9 8 7 6 5

ISBN 0-13-220732-X 01

Prentice-Hall International (UK) Limited, *London*
Prentice-Hall of Australia Pty. Limited, *Sydney*
Prentice-Hall Canada Inc., *Toronto*
Prentice-Hall Hispanoamericana, S.A., *Mexico*
Prentice-Hall of India Private Limited, *New Delhi*
Prentice-Hall of Japan, Inc., *Tokyo*
Prentice-Hall of Southeast Asia Pte. Ltd., *Singapore*
Editora Prentice-Hall do Brasil, Ltda., *Rio de Janeiro*
Whitehall Books Limited, *Wellington, New Zealand*

PREFACE

As the title suggests, this book was written to provide the reader with an introduction to the fascinating field of behavioral pharmacology; the systematic study of the effects of drugs an behavior and the ways in which behavioral principles can help us understand how drugs work. Because research in this field is done in a variety of animal species, I have included data from experiments on both humans and nonhumans. This represents something of a departure from the usual approach to this material, but it should not deter the serious student. The field has developed to the point where it is impossible to fully understand human drug use without some knowledge of the research that can only be done on nonhuman species. Rather than make the material more difficult, understanding the research on nonhumans provides a perspective that simplifies the complexities of human drug use.

The book has two parts. The first five chapters are on "basic concepts" and are there to provide sufficient background to understand the remaining nine chapters. These are devoted to different drugs or classes of drugs. The reader is invited to pick and choose from these first five chapters and fill in gaps in their knowledge. Those with an introductory psychology course will probably be able to skip the chapter on the behavioral analysis of drug effects and those with some experience in medicine, pharmacology, physiology, or nursing will be able to omit the chapters on neurophysiology, and on absorption and distribution and excretion. These basic concepts chapters do not contain extensive citations of the literature and are provided as a background and as an explanation of the concepts that are used in the second part of the book.

The second part of the book consists of nine chapters on specific drugs and drug classes. Each chapter is organized in the same way. It starts with a discussion of the sources of the drug and the ways it is prepared for use. There is

also a short history which, in addition to being entertaining, is designed to provide some insight into the origins of current attitudes and legislation concerning the drug. The routes of administration, absorption, and distribution and excretion/metabolism of each drug are discussed along with a synopsis of what is known about its site and mechanism of action. Each chapter also has a section on effects on the body, effects on sleep, effects on the behavior and performance of humans and nonhumans, withdrawal symptoms, tolerance, self-administration, harmful effects, and finally, treatments. This similarity in layout is designed to make possible quick comparisons between drugs, and to use the book as a handbook for quick reference to specific drugs and specific drug-related phenomena.

These nine chapters are supported fully with literature citations in the manner used by most scientific journals. The particular works cited were not chosen to support each point, but were selected as sources for further study. For this reason they tend to be book chapters or literature reviews, but original research reports have been used where necessary.

A glossary is provided at the end of the text. While this glossary is primarily intended as a support for users of the book, I have attempted to make it sufficiently extensive so that it can be used as a general dictionary for the field.

This is the first book I have attempted to write and the experience has been exhausting, frustrating, time consuming, and above all, fun. It has not been, nor could it have been done in isolation, and I have to acknowledge the generous assistance of the many people who have contributed their time and knowledge to correcting and improving fact, grammar, and style. These include Gerard Martin, Bow Tong Lett, Sam Revusky, Marvin Krank, Harry Taukulis, Wayne Dornan, J. C. LeCaille, Edna McKim, Muriel Vogel-Sprott, Peter Harley, John Scott, Anne Storey, Ken Roberts, and many others including the hundreds of students who have had to use various versions of this manuscript as a text for Psychology 2800 over the last few years. I also wish to acknowledge the excellent art Work of Gill Campbell of Woof Design and her interest and cooperation in this project.

W. A. M.
St. John's, December 7, 1984

CONTENTS

chapter 1

RESEARCH DESIGN AND DRUG DOSAGES, DOSE RESPONSE CURVES, AND INTERACTIONS

All scientific experimentation can be thought of as a search for a relationship between events. In behavioral pharmacology the researcher is usually trying to find out the relationship between the presence of a drug in an organism and changes that occur in the behavior of that organism. In most true experiments, one of these events is created or manipulated by the experimenter and the other event is measured. The manipulated event is called the *independent variable* and the observed event is called the *dependent variable.* The independent variable in behavioral pharmacology is usually the amount of drug put into the organism; that is what the researcher manipulates. The dependent variable is usually some change in the behavior of that organism and this is what the researcher measures. The next chapter discusses some of the more commonly used measures of behavior or dependent variables.

EXPERIMENTAL RESEARCH DESIGNS

Experimental Control

It is not enough to give a drug and observe its effect. For an experiment to be meaningful, the experimenter must be able to compare what happened when the drug was given and what would have happened if the drug had not been given. In other words, the experiment needs a *control.* A controlled experiment is one in which it is possible to say with some degree of certainty what would have happened if the drug had not been given. This permits comparisons to be made between drug and nondrug states. For example, a researcher could give several subjects each a pill containing THC, the active ingredient in marijuana, and observe that everyone tended to laugh a great deal after-

ward. These observations would not be worth much unless the researcher could demonstrate that the increased laughter was a result of the drug, and not a result of the subjects' expectation, or of nervousness about being observed, or of some factor other than the presence of drug in the body. As with most behavioral experiments, there are many factors that could influence the results and so it is essential to be sure that the drug, and not something else in the procedure, caused the laughter.

The only truly reliable way to do this experiment and eliminate all possible causes of the laughter apart from the drug, would be to have a time machine, and, after the experiment, go back and give the same students identical pills not containing any drug. Comparisons could then be made between the amount of laughter with and without the drug, since all other factors (the subjects, the situation, the time of day, and so on) would be the same.

Since there is no such thing as a time machine, the behavioral pharmacologist must compare the behavior of a drugged subject with either a) the drug-free behavior of that subject under similar conditions; or b) the behavior of other drug-free subjects under similar conditions.

The first alternative is called a *within-subject* design. In this strategy, careful observations are made of a subject's behavior under specific conditions and when the behavior appears to be stable and predictable it is then possible to give the drug and make comparisons between drugged and nondrugged behavior. In other words, subjects serve as their own control.

Let us say, for example, we are interested in the effect of amphetamine on feeding behavior of rats. In a within-subject design, the researcher carefully measures the daily food consumption of several rats until the measures are constant for each animal. The researcher then injects a dose of amphetamine into each rat and measures food consumption for that day. Meaningful comparisons can now be made between food consumption on drug and nondrug days since the researcher has a pretty good idea how much each animal would have eaten if it had not been given the drug.

This experiment could also be done using a *between-subject* design. In this, a number of rats are randomly assigned to two groups. One group, the experimental group, would get the amphetamine and the other, the control group, would not get any drug. The food consumption of both groups could then be compared.

Comparisons of Between- and Within-Subject Designs. The type of design used by the behavioral pharmacologist is usually determined by the type of dependent variable being measured in the experiment. If the measure is stable from day to day, like eating, within-subject designs can be used, but if the dependent variable is subject to systematic change, then the researcher is forced to use a between-subject design. Exploratory behavior is a good example of such a measure; on the first exposure to a new cage a rat will usually spend a considerable time moving around and exploring, but on the second day it may be habituated to the new surroundings and it may just sit and lick its whiskers. A within-subject design could not be used here because the behavior changes from day to day and we would not know whether the change was due to the drug or to habituation. A between-subject design would be appropriate because both the experimental and control groups could be compared on the first exposure to the new cage and habituation would not be a factor.

The difficulty with the between-subject design is that responses of individuals may vary a great deal. By chance we may get very curious rats in one group and very lazy rats in another. The differences in groups would then be due to differences in rats and not to the effects of the drug. We could get around this difficulty by having large groups, which would decrease the likelihood that all the curious or lazy rats would end up in one group. It would also mean much more work and have the additional disadvantage that the final results would be in terms of group averages, which sometimes hide important information that is more apparent in work with individual subjects.

The advantage of the within-subject design is that more perfect control conditions can be achieved since each subject is its own control. The disadvantage is that it can only be used with behavioral measures that are not likely to change when repeated. Within-subject experi-

ments usually take more time, but they do not require as many subjects.

Statistical Testing. In some within-subject and most between-subject designs, some sort of statistical tests are needed to determine the probability of differences observed between drug and nondrug measures. Such tests are necessary because differences could be due to chance variations from day to day and from subject to subject. When a researcher finds a difference in the means of the groups, a statistical test can tell how often by chance such a difference is likely to occur if there were no drug effect. Box 1-1 gives a numerical example of how statistical tests are used.

Placebo Controls. To be completely useful, a control condition must be as similar as possible to the experimental condition except for one variable: the presence or absence of the drug. In the example given above, where the

BOX 1-1 An example of the use of statistical tests

A mythical experiment was done to determine the effect of amphetamine on food consumption in rats. The experiment was a between-subject design with 10 rats in each group. Both groups were treated identically except that the rats in one group were given amphetamine before eating and the rats in the other group were given a placebo injection of the vehicle normal saline (see page 22, chapter 3). The researcher found that the amphetamine group ate a mean of 16.7 g of food and the control rats ate a mean of 20.5 g of food. On the basis of this difference could the experimenter conclude that amphetamine reduced food intake? To answer this question a statistical test is needed.

The following table gives the actual food consumption for each rat in the experiment. The most appropriate statistical test for this type of experiment would be what is known as a "t" test. This test takes into account the variability in each group, and on the basis of certain assumptions, it can tell the experimenter how many times the experiment would have to be repeated to get this big a difference in the means just by chance.

In this case the "t" test tells the experimenter that if the drug had no effect and the experiment was done 100 times, there would be a difference this big between 5 and 10 times, just by chance. This is not normally good enough. Most behavioral researchers insist that their results be explainable by chance no more than 5 times in 100, or as they say, with a probability less than 5 percent ($p < .05$). If the probability level is greater than 5%, the result is generally considered to be negative. If you read original research reports you will see the results of statistical tests are reported something like this: ($t = 2.09$ $df = 18$, $p < .05$). The first two numbers are values associated with the statistical test and the final number is the probability level.

There are many different types of statistical tests for many different research designs. They all, however, end up telling you the same thing: how often you would expect to get the results by chance if there were no drug effect (Ferguson, 1966).

When using a within-subject strategy, a statistical test is sometimes not necessary. Most research using operant techniques examines the behavior of three or four experimental subjects in great detail and under carefully controlled experimental conditions. Nondrugged performance is very reliable and so when the drug is given it is readily apparent whether there are any drug-produced changes in behavior and statistical analyses are not necessary.

Control Group		Experimental Group	
rat no.	*food eaten*	*rat no.*	*food eaten*
1	18g	11	17g
2	22g	12	14g
3	23g	13	12g
4	17g	14	25g
5	28g	15	15g
6	20g	16	16g
7	16g	17	20g
8	22g	18	21g
9	21g	19	13g
10	18g	20	11g
mean	20.5g		16.7g

effect of amphetamine on rats' eating was determined, the control procedure could have been improved. As you recall, we had two groups; one was injected with amphetamine and the other was not injected at all. It is quite possible that the anxiety of being stuck by a needle suppressed eating by itself and the amphetamine had nothing to do with the results. For this reason, behavioral pharmacologists always use a control condition that involves the injection of the vehicle alone. (See page 22, chapter 3.) This means that on control days in within-subject designs, and for control subjects in between-subject designs, an injection of normal saline would be given. Subjects in the experimental group, or on drug days, would be treated identically, except they would have the drug dissolved in the saline.

Such careful controls are especially important with human subjects because of a phenomenon known as the *placebo effect.* A *placebo* is a totally inert substance which causes no physiological change, but is administered as though it were a medicine. If people believe they are getting a drug that will have a specific effect, they will frequently show that effect even though the drug does not cause it. This placebo effect makes careful control an absolute necessity when evaluating the clinical effectiveness of newly developed drugs because patients will frequently show an effect they expect the drug to have. For example, let us suppose that we are testing a new pain reliever. We go to a hospital and give the drug to a group of patients who are in postoperative pain and tell them that this new drug should relieve their distress. The next day we find that 68 percent of the patients report that their pain was relieved. By itself, this is not a useful experiment because we do not know how many patients would have reported the same thing without the drug. To do this experiment the proper way, it would be necessary to have two groups of patients. While both groups would be told they were getting a pain reliever, only one group would get the new drug and the other would be given an identical pill containing only sugar. The next day, pain ratings would be taken from all the patients and comparisons could be made.

Further precautions need to be taken in an experiment of this nature. It has been known for some time that an experimenter can influence the outcome of research without knowing it. For example, if the researcher knows which patients have been given a placebo, the researcher might unconsciously change the manner in which the patients are interviewed, or, even make systematic mistakes in recording data. To eliminate this possibility, it is usual to conduct the experiment so that neither the doctors or nurses giving the drug, nor the researchers interviewing the patients for the pain ratings know which patients were in which group. This procedure is called a *double blind* and is essential because it eliminates the possibility of any experimenter bias effects.

NONEXPERIMENTAL RESEARCH

A good deal of what we know about drugs is a result of research that does not involve experiments. As explained earlier, experiments attempt to find relationships between two events, a manipulated event and a measured event. Nonexperimental research looks for a relationship between two measured events. A good example is the discovery of a relationship between smoking during pregnancy and infant mortality. It was shown some time ago that there was a higher rate of infant death among babies born to women who smoked during pregnancy than among babies born to nonsmoking mothers. (See chapter 9.) In this research nothing was manipulated, there was no independent variable. The two events, smoking and infant mortality, were measured and found to be related.

One major difficulty with this sort of finding is that we cannot assume a causal relationship between the two related events unless a true experiment is done. We know that children born to smoking mothers are more likely to die, but we cannot conclude that smoking *causes* the infant deaths. The relationship might be due to some third factor that causes both events. For example, it may be that women smoke because they have a biochemical imbalance that causes their bodies to need the nicotine in cigarettes. This imbalance might also be responsible for the higher infant mortality rates. The only way we

can be sure that the smoking causes the infant mortality is to do a true experiment by finding two groups of pregnant women and forcing one group to smoke. If there is a difference in infant mortality between the two groups we are in a good position to propose a causal relationship. Of course, such an experiment would be out of the question on ethical grounds and it could never be done with humans. For this reason we are going to have to be satisfied with relational rather than causal data on many issues of drug effects in humans.

NEGATIVE RESULTS

The methodology of science has been developed to answer questions about relationships between events and if research, either experimental or nonexperimental, finds a relationship, then this is useful information. The reverse, however, is not true. It is almost impossible to prove something does not exist. Just because an experiment does not find a relationship, it does not mean that the relationship is not there. Experiments can fail for a number of reasons; the researchers may not be using the right experimental subject, they may not be measuring the dependent variable accurately, they may not be using an appropriate dose of the drug, or the relationship they are looking for might not exist. With negative results, it is impossible to know which explanation is the correct one.

For this reason we can never say such things as "smoking does not cause cancer" or "smoking marijuana does not lead to the use of other drugs." Instead, careful researchers say things like, "There is no evidence that shows . . . " This is a much more cautious but more accurate way of putting things.

NAMES OF DRUGS

One of the more confusing aspects of drugs is understanding their names because most drugs have at least three names, and it is not always apparent which name is being used at any given time.

Chemical Name

All drugs have a *chemical name.* This is in formal chemical jargon, and a chemist can usually tell by looking at the name what the molecule of the drug looks like. Here is the chemical name of a drug: "7-chloro-1,3-dihydro-1-methyl-5- phenyl-2H-1, 4-benzodiazepin -2-one." As you can see, it is full of chemical terminology, letters, and numbers. The numbers refer to places where different parts of the drug molecule are joined. Just to make things more complicated, there are different conventions for numbering these parts of the molecule. This means that the same drug might have a different name if a different convention is used.

Generic Name

Once a drug becomes established, its chemical name is too clumsy and so a new, shorter name is made up for the drug, the *generic name* or *nonproprietary name.* The generic name for the drug whose chemical name we just struggled through is "diazepam." You can see that the generic name bears some resemblance to the chemical name. There are conventions for making up generic names which are handy to know because they are clues to the nature of the drug. For example, most barbiturate drugs end in "al," like "secobarbital," and most local anesthetics end in "caine," as in "procaine."

For the most part, textbooks and scientific discussions of drugs use the generic name as does this book.

Trade Name

When a drug company spends many millions of dollars to invent and develop a new drug, it can patent the drug for a number of years so that no other company can sell it. The drug company does not sell the drug under its generic name. Instead, it makes up a new name called the *trade name* or *proprietary name.* The trade name for the drug we have been discussing is "Valium." After the patent expires, other companies can sell the drug, or they can make it under license from the owner of the patent, but they frequently sell it under different trade

names. This means that there can be many different trade names for the same drug.

Because drug companies sell their products under trade names, people in the medical profession are most familiar with these names and are most likely to use them. So if you are given a prescription for a drug by a physician and you are told the name of the drug, you may not be able to find it listed in this or any other text that goes by generic names. Trade names can be distinguished from generic names because they are usually capitalized.

DESCRIBING DOSAGES

All of modern science uses the metric system and drug doses are nearly always given in *milligrams* (*mg*). A milligram is 1/1000 of a gram (there are a little over 28 grams in an ounce).

In research papers, doses are usually reported in terms of milligrams per kilogram of body weight, for example, 6.5 mg/kg. (A kg is equal to 2.2 pounds.) If the same amount of a drug is given to individuals of different sizes, the drug will reach a different concentration in the body of each individual. To ensure that the drug is present in the same concentration in the brains of all subjects or patients, different doses are given according to body weight.

Reporting doses in this manner also helps when comparing research on different species. If you account for such other factors as metabolic rate, a dose of 1.0 mg/kg in a mouse will be comparable to a dose of 1.0 mg/kg in a rat.

Dose Response Curves

In order to get a true picture of the effect of a drug it is usually necessary to give a range of doses of the drug. The range should cover a dose so low that there is no detectable effect and doses so high that increases have no further effect. It is usual to plot the effect of this range of doses on a graph with the dose indicated on the horizontal axis and the effect on the vertical axis. This type of figure is called a *dose response curve* (*DRC*). Figure 1-1 gives a typical DRC. It shows the effect of caffeine on the mouse's rate of responding on an FI schedule.

Note that the scale on the horizontal axis is graduated logarithmically. It is generally found that a small change in low doses can have a big effect, but an equally small change in a large dose has no effect. Plotting doses on a log scale allows a wide range of doses to be reported and permits greater precision at the low end of the dosage range. Log scales became common when it was found that many physiological effects of a drug showed up as a straight line when plotted on a log scale.

In the example just used, the drug effect was

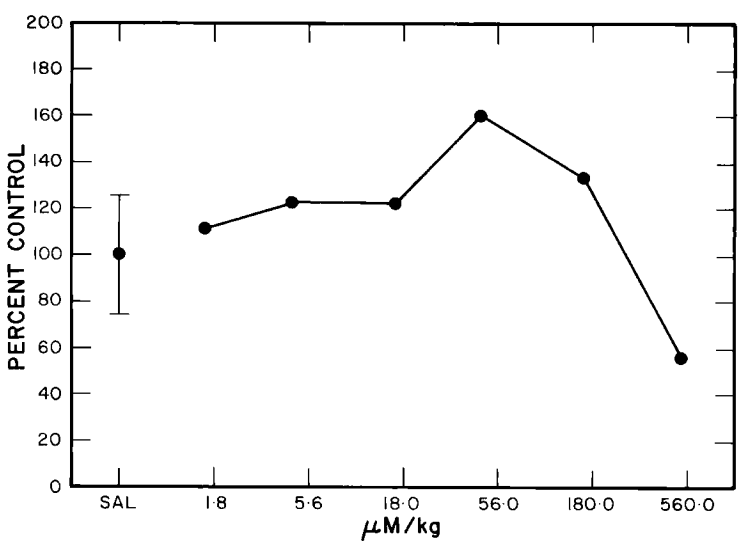

FIGURE 1-1. The dose response curve for the effect of caffeine on rate of responding of a mouse being reinforced on an FI schedule with food. (Adapted from McKim, 1980.)

a measure of response rate, but there are other types of DRCs where the effect is a discrete binary variable rather than a continuous one. For example, we could not use this type of curve if we wanted to report a DRC for effectiveness of a drug as an anesthetic. Subjects are either anesthetized or they are not. If the vertical axis simply read "yes" or "no," this would not give us any sort of a curve. When a binary variable is used, DRCs are constructed differently.

This sort of research is handled by working with groups of subjects. Each group is given a different dose of the drug and the percent of subjects in each group that shows the effect is then plotted. An example of this sort of DRC is given in Figure 1-2. This hypothetical experiment is designed to establish the DRC for loss of consciousness and the lethal effects of a new drug, endital. In this experiment there are twelve groups of rats. Each group is given a different dose of endital starting from 0.0 mg/kg, a placebo, to 110 mg/kg. The vertical axis of the graph shows the percentage of rats in each group that showed the effect. The first curve shows how many rats lost consciousness and the second curve shows the percentage of rats in each group that died.

ED_{50} and LD_{50}. A common way of describing these curves and comparing the effectiveness of different drugs is by the *ED_{50}*. The ED_{50} is the *median effective dose,* that is, the dose that is effective in 50 percent of the individuals tested. The ED_{50} for losing consciousness for endital in Figure 1-2 is 40 mg/kg. By checking the next curve you can see that the dose that killed 50 percent of the rats was 80 mg/kg. This is known as the *median lethal dose* or the *LD_{50}*.

Drug Safety. When new drugs are being developed and tested it is common to establish the LD_{50} and the ED_{50} to give an idea of the safety of a drug. Obviously, the further the lethal dose is from the effective dose, the safer the drug. The *therapeutic index* (*TI*) is sometimes used to describe the safety of a drug. This is the ratio of the LD_{50} to the ED_{50}; $TI = LD_{50}/ED_{50}$. The higher the index the safer the drug.

DRUG INTERACTIONS

When two drugs are mixed together, their effects can interact in several ways. If the effects of one drug diminish the effect of another this is called *antagonism.* Drug antagonism is established by plotting two DRCs, one for the drug alone and a second for the drug in the presence of the other drug. If the DRC is shifted to the right by adding the new drug then this indicates antagonism between the drugs.

If adding the new drug shifts the DRC to the

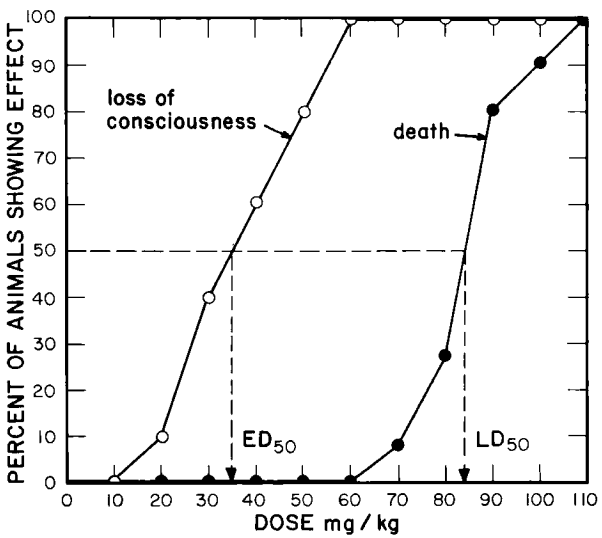

FIGURE 1-2. Results of a hypothetical experiment in which twelve groups of rats were each given a different dose of drug ranging from 0.0 to 110 mg/kg. One curve shows the percent of animals in each group that lost consciousness and the other curve shows the number of rats that died.

left, this indicates the drugs have an additive effect. If drugs have an effect together that is greater than you might expect simply by adding their effects, this is called a *super additive* effect or *potentiation*. It is not always obvious whether a drug interaction is additive or super additive, but there is one situation where the distinction is clear. If one drug has no effect alone, but it increases the effect of a second drug, this is clearly potentiation.

Careful determination of how drugs interact can tell us a great deal about the mechanism of drug action. For example, if we give a drug that is known to block a certain type of receptor and we find that it antagonizes a specific effect of another drug, then we can guess that the second drug probably interacts with that type of receptor to produce that effect (see chapter 4).

CHAPTER SUMMARY

1. Scientific experiments consist of an *independent variable* that is manipulated by a researcher and a *dependent variable* that is measured. The aim of research is to determine whether changes in the independent variable cause changes in the dependent variable. In most experimental research in behavioral pharmacology, the independent variable is the presence of drug in the body and the dependent variable is a change in behavior.
2. To determine whether a drug has an effect on behavior, a comparison must be made between behavior when the drug has been given and behavior when the drug was not given. In other words, every experiment must have a *control*. In order to make this comparison, researchers can compare the behavior of a subject given the drug with behavior of the same subject not given the drug. This is a *within-subject control* design. Another alternative is to compare the behavior of a subject given a drug with a different subject not given the drug. This is a *between-subject control* design.
3. A within-subject control design has the advantage that it can eliminate any error effects due to variations in subjects, and it usually uses fewer subjects. The disadvantage of the within-subject design is that it generally takes longer and cannot be used to study behavior that changes systematically over time.
4. The advantages of the between-subject design are that it can be used to study behaviors that change when repeated and it can often be faster. The disadvantages are that error can be introduced by differences in individual subjects, and this usually means that large groups of subjects must be used.
5. In most experiments, differences are found between experimental and control conditions. These differences may be large or very small. In order to determine whether the differences mean anything, a statistical test is often used. Statistical tests tell the researcher how frequently there would be differences as large as in the experiment if there was no effect of the drug and all differences were due to chance alone. If differences observed would be expected by chance less than 5 times in 100 ($p < .05$), it is presumed that the differences are due to the drug, not chance.
6. Treatment of control subjects in an experiment should be as similar as possible to treatment of experimental subjects. For this reason control subjects are usually given a *placebo,* an inactive substance administered exactly the same way as the drug. This controls for differences due to the act of drug administration.
7. Most drug experiments, especially with human subjects, should be conducted in a *double-blind* manner: neither the subjects nor the researchers themselves should be aware of which subjects are in the control group and which are actually receiving the drug. This controls for both placebo effects and experimenter bias effects.
8. In *nonexperimental* drug research, the aim is to find a relationship between two measured variables: the researcher does not manipulate any variables. The disadvantage of nonexperimental research