CENTRAL NERVOUS SYSTEM PHARMACOLOGY: A SELF-INSTRUCTION TEXT
Second Edition

Donald E. McMillan, Ph.D.

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Donald E. McMillan, Ph.D.
Professor and Chairman, Department of Pharmacology,
University of Arkansas College of Medicine, Little Rock

Little, Brown and Company
Boston

Second Edition

Library of Congress Catalog Card No. 78-71218

ISBN 0-316-56242-4

Printed in the United States of America

PREFACE

Since the publication of the first edition of this self-instruction text five years ago, there have been a number of exciting new developments in central nervous system pharmacology. Our knowledge about the neurochemistry of the central nervous system (CNS) and how it is altered by drugs has advanced rapidly. The discovery of important new therapeutic agents (some of which were relatively unknown five years ago but which now are used widely in the clinic), the description of the fetal alcohol syndrome, the understanding of the relationship of mild analgesic action to the prostaglandins, the discovery of an endogenous peptide in the brain with morphinelike action, and changes in patterns of drug abuse are only a few of the developments that necessitate a new edition.

The first edition was designed for use as a subunit in a general pharmacology course. Depending on the depth of instruction desired, the text could be used either as the major teaching device in a short course or as a foundation upon which supplemental material could build in longer courses of greater depth. The target groups were dental, pharmacy, and medical students who were taking a first course in pharmacology. Because CNS pharmacology usually is not taught at the beginning of the course, it was assumed that the students would already be well versed in the general principles of pharmacology and in the concepts of neurotransmission from earlier parts of their courses, so no material on those subjects was included in the self-instruction text. Although the first edition was used widely in medical, dental, and pharmacy schools, it was unexpectedly popular with other groups who were not using it as part of a pharmacology course. The first edition has been used in the training of psychiatric nurses and graduate students in clinical and experimental psychology, for example, besides being used by psychiatry residents for a brief review of the effects of psychiatric drugs.

Because the first edition reached such a diverse audience, not all of whom had an opportunity to study other aspects of pharmacology, I think that there is a need for additional chapters on the general principles of pharmacology and on synaptic transmission. The new chapters are not intended as an in-depth study of the topics; rather, they are added to enable students not exposed to those areas in a formal course to obtain at least an introduction to some important concepts necessary to the study of CNS pharmacology. Students who have in-depth knowledge of the general principles of pharmacology and synaptic transmission might wish to skip the early chapters.

Another addition to the second edition is the chapter on the emerging discipline of behavioral toxicology. As more and more toxic chemicals enter our environment, it has increasingly become recognized that many of them affect the CNS and produce behavioral changes. The final chapter of the text presents a brief introduction to that area.

Most of the chapters have undergone revision, and many of them have been completely reorganized. I only hope that the second edition meets with the same acceptance that students and colleagues were so kind to grant the first.

D. E. McM.

Little Rock, Arkansas

ACKNOWLEDGMENTS

I thank Dr. John Gatzy and Dr. David Leander, who reviewed several chapters in this edition and made many helpful suggestions. I am grateful to Peggy Hansen for the rapid and accurate typing of several drafts of each of the chapters. Finally, I thank my children, David and Pamela, and my wife, Jerry, for their patience and support during the preparation of the revision of this text.

D. E. McM.

GUIDELINES FOR USE OF THE SELF-INSTRUCTION TEXT

This self-instruction text has been designed to help the student learn some basic principles of CNS pharmacology. The information is presented in a narrative style in an effort to make it more interesting than the usual frame-by-frame presentation; however, the student interacts with the material in an active manner, as in other forms of self-instruction.

The student should cover the numbered answers in the right-hand margin of the page with a small strip of paper and then begin reading the text. When the student comes to a blank space, the answer that the student thinks is correct should be *written* in the blank space. After writing an answer in the blank space, the student should uncover the correct answer in the right-hand margin immediately and check to see if his answer matches the correct one. The student's answer will be considered correct if the word or phrase written in is approximately equivalent to the correct answer, even if it is not exactly the same as the correct answer. If the answer is correct or equivalent to the correct answer, the student should again cover the answers and proceed with the text. If the answer is wrong, the incorrect answer should be crossed out or erased and the correct answer placed in the blank space before proceeding. It is very important that the answers be *written* in the spaces provided. Only in this way will the student be able to master some of the long and difficult drug names.

The self-test at the end of each chapter serves at least two purposes: first, it enables the student to evaluate how well he or she has mastered the material presented in the chapter, and, second, it provides a brief review of some of the more important points in the chapter. Students with some previous background in CNS pharmacology may wish to try the self-test before reading the chapter. Students who are able to fill in the correct answers to the self-test without going through the text material should use their time to study textbooks on pharmacology that present more details and applications of the basic principles of CNS pharmacology. I hope that those who are encountering CNS pharmacology for the first time will be able to use this self-instruction text to obtain a body of information sufficient to pursue the study of CNS pharmacology in greater depth.

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1. INTRODUCTION TO CNS PHARMACOLOGY

From 1946 to 1955 the number of psychiatric patients in mental hospitals in the United States increased by more than 10,000 patients per year. By 1955 these patients filled about half the hospital beds in the United States. In 1955 the use of tranquilizers became widespread, and in 1957 antidepressant drugs were introduced. From 1955 to 1973 the number of patients in mental hospitals in the United States fell from a high of 559,000 to the present level of 200,000, despite a continuing increase in admission rates. These statistics show the tremendous impact of tranquilizers and antidepressants on clinical practice.

There are other impressive statistics worth considering because they emphasize how drugs that act on the central nervous system (CNS) permeate practically every phase of our daily lives. For example, in the United States about one-third of all prescriptions for outpatient drugs are for psychoactive drugs. More than 12,000 *tons* of aspirin are consumed in the United States each year. There are probably 1.5 million diagnosed epileptics in the United States, most of whom require some kind of medication. Perhaps 3 to 4 percent of all children are hyperkinetic, and many of them are taking amphetamines. Two-thirds of the adult population in the United States use ethanol, and the number of alcoholics in the United States is presently estimated to be more than 10 million. A majority of Americans between 18 and 25 years of age have used marihuana, and among young people, its usage seems to be increasing. Equally astounding statistics for many other drugs that affect the central nervous system could be cited, but it should already be clear that drugs that affect the CNS are used so widely and so frequently, both for therapeutic and recreational purposes, that it would be very hard to imagine a world without them.

In this introductory chapter, a brief overview of drugs with effects on the CNS will be presented, along with some generalizations about drug-behavior interactions.

By the time that you finish this chapter, you should be able to:

1. Recognize some of the classes of drugs that have effects on the CNS.
2. List some ways in which drugs and behavior interact.

The first group of drugs that we will be studying are the *tranquilizers*. Actually, the tranquilizers consist of two distinct groups of drugs. These groups have often been referred to as *major* and *minor* tranquilizers, but because the words "major" and "minor" imply to some people that the major tranquilizers are somehow more important than the minor tranquilizers, we shall not be using these terms. Instead, we will refer to these drug groups as *antipsychotic* and *antianxiety* agents, respectively.

The psychoneurotic patient suffers from a constellation of problems, of which the subjective feeling of anxiety is most characteristic. As you might expect, the group of tranquilizers called the anti-[1]_____ agents are used to treat psychoneurotic patients. Psychotic patients, in contrast to psychoneurotic patients, may show little evidence of anxiety. Their behavior is characterized by thought disorders, extreme swings in mood, regressive behavior, and loss of contact with reality. Perhaps the best-known (but least understood) psychotic disorder is schizophrenia. The tranquilizers used to treat schizophrenia are the anti-[2]_____ drugs. The antipsychotic drugs are also used to control the high rate of psychomotor behavior and emotional lability of some manic-depressive patients, although their use is being replaced by the administration of lithium ion for many patients.

[1] anxiety

[2] psychotic

Depression is usually considered as a clinical entity, although it sometimes is a sign of psychoses and all of us experience so-called normal depression as a reaction to unhappy experiences in life. Antipsychotic drugs can be effective in the treatment of depression, but two different classes of *antidepressant* drugs are used more often in the treatment of

depression. These anti-[3]_____ drug classes are the *tricyclic antidepressants* and the *monoamine oxidase inhibitors.* They differ from the CNS stimulant drugs in that the stimulants elevate the mood of normal people, but antidepressant drugs have little effect on the mood of normal people and exert their mood-elevating effects

only on [4]_____ people.

[3] depressant

[4] depressed

The next group of drugs that we will be studying are the *analgesics,* the drugs used to control pain. Again, there are two classes, strong analgesics and mild analgesics. The strong analgesics are used to control severe pain. They have a number of drawbacks, perhaps the most serious of which is that they are subject to abuse. Morphine is the best-

known [5]_____ analgesic that is used clinically. The mild analgesics, such as aspirin, are used to control less severe pain. Some are very useful in controlling fever and inflammation as well.

[5] strong

Convulsions can result from a host of causes, including brain damage, fever, and the withdrawal of some drugs. We will be studying the drugs used to control convulsions, or

anti- [6]_____ drugs, primarily in terms of their use in the treatment of epilepsy. There are a number of kinds of epilepsy, and a classification system for epilepsy will be presented in a later chapter.

[6] *convulsant*

Drugs used to prepare a patient for sleep or to induce sleep are called *sedative hypnotics.* These drugs are similar in many respects to the antianxiety agents; for example, both

antianxiety agents and [7]_____ decrease tension and anxiety, relax muscles, and give the patient a feeling of well-being. With the antianxiety agents, however, the objective is to achieve this state without putting the patient to sleep, whereas with the sedative hypnotics, the primary objective usually is to induce

[8]_____ .

[7] sedative-hypnotics

[8] sleep

There are a number of *alcohols* that have effects on the CNS. Certainly the best-known alcohol is ethyl alcohol, or *ethanol,* which is present in alcoholic beverages. Like the sedative hypnotics, ethanol has many effects on the CNS that resemble those of the

anti-[9]_____ agents, but ethanol also has other pharmacologic effects of interest Although the most widely used alcohol is

[9] anxiety

[10]_____ by a wide margin, methyl alcohol and isopropyl alcohol are of some toxicologic interest.

[10] ethanol, ethyl alcohol

Tremors, spasticity, muscle tension, and rigidity are among the neurologic signs seen in clinical disorders such as cerebral palsy, Huntington's chorea, and parkinsonism. Several types of drugs are used to treat these diseases, and some of them will be discussed later. As is the case with most drugs that affect the CNS, these drugs do not cure the disease, but they help to control the neurologic problems produced by the disease.

Another group of drugs that will be considered are the *general anesthetics.* Before the introduction of these agents into the clinic, some kinds of surgery that are routine today were impossible. There are several ways of classifying general anesthetics. One way is on the basis of their route of administration Many drugs that depress the CNS to produce a *loss of consciousness, amnesia, and analgesia are gases or volatile liquids, so the drugs can* be administered by inhalation. When an anesthetic drug enters the bloodstream through the lungs, it is easy to control the depth of anesthesia by controlling the amount of drug in the inspired air. This is a major advantage of giving an anesthetic by

[11]_____. Anesthetics given by injection are usually administered

[11] inhalation

into the veins, hence the term intra-[12]_____ general anesthetics. Although it is more difficult to control the depth of anesthesia with these drugs, the intravenous anesthetic thiopental is very useful for inducing anesthesia because it has an extremely rapid onset of action.

[12] venous

This text devotes three chapters to drug abuse, including chapters on *opiates, CNS stimulants* and *depressants,* and *hallucinogens.* The clinical effects of the opiates are discussed in detail in the earlier chapters, because of their widespread use as strong

[13] _____. CNS stimulants and depressants are also discussed in early chapters as therapeutic agents before consideration of their abuse potential, but, because the hallucinogens have no established therapeutic usefulness, the pharmacology of these drugs is discussed only in connection with their abuse. The hallucinogens consist of a group of chemically diverse agents including marihuana, lysergic acid diethylamide (LSD), and many others. What these agents have in common is that at some doses they are able to produce sensory experiences that do not correlate with sensory input. Such experi-

[13] analgesics

ences are called [14] _____, and therefore the drugs are called *hallucinogens.*

[14] *hallucinations*

The final chapter is concerned with certain chemicals in our environment that affect the CNS. In this brief survey, attention will be focused on heavy metals, pesticides, and carbon monoxide, although a host of other chemicals in the environment also have effects on the CNS.

Drugs that act on the CNS produce behavioral changes in organisms. Our knowledge about the exact mechanisms through which drugs affect behavior is limited, for a number of reasons. First, many of the drugs that modify behavior are relatively new, and basic scientists and clinicians have not had a very long time to study these drugs. Second, the CNS is exceedingly complex. How it controls behavior and how the control of behavior by the CNS is modified by drugs are not well understood. Finally, the scientific study of behavior is a recent development, and its application to the study of drug-behavior interactions is only beginning.

Despite the fact that behavioral pharmacology is still at an early stage of development, there are several generalizations that can be made about the effects of drugs on behavior. One of these generalizations is that the effect of drugs on behavior is determined in part by the environmental circumstances in which the drugs are given. Thus the clinician who shows enthusiasm for the drug regimen and provides a supportive therapeutic atmosphere

is likely to obtain [15] _____ therapeutic results than the clinician who has little confidence in the drug treatment.

[15] better

A second important generalization about the behavioral effects of drugs has been referred to as the "law of initial value." What this means is simply that the effects of drugs depend on the *initial value* of behavior — in other words, the ongoing rate of behavior at the time a drug is given. The law states that when a drug increases behavior, the change from the initial level of behavior will be smaller when the initial value is high, and when a drug decreases behavior, the change will be smaller when the initial value is low. Conversely, a drug that increases behavior will produce its largest effects when the initial value of behavior is low, and a drug that decreases behavior will produce its largest

effects when the initial value is [16] _____. Under some conditions, the initial value may cause the "usual" effect of a drug to disappear or to be reversed; for

[16] high

example, amphetamine given to overcome fatigue may [17] _____ the behavior of a fatigue patient, but, in contrast, amphetamine may also

[17] increase, stimulate, etc.

[18] _____ the high rate of motor activity of a hyperactive child. Similarly, a tranquilizer may be very useful in decreasing the motor activity associated with a manic episode but have little effect on the motor activity of a depressed

[18] decrease, depress, suppress, etc.

patient. Thus, the initial value of a patient's ongoing [19] _____ can contribute to the drug's effect on that behavior.

[19] behavior

A third generalization that can be made about the effects of drugs on behavior is that these effects depend on the dose of drug. This fact may seem obvious, but it is a point that is often ignored in the clinical literature. One sometimes sees comparisons made between drugs when only a single dose of each drug has been studied. One cannot place

much faith in these studies, because it is not known whether the single dose level was

[20] _____ for changing the behavior measured.

[20] optimal, appropriate, adequate, etc.

Generally, drugs such as tranquilizers and antidepressants are thought to exert their effects by reducing such drives as anxiety, fear, and guilt. Experimental animal studies, however, have not provided strong evidence for this hypothesis. The effects of an antipsychotic agent such as chlorpromazine, for example, do not seem to depend on whether an animal is motivated to respond because of food deprivation or because its responses will allow it to avoid a painful electric shock. Thus, tranquilizers do not seem to affect

negatively motivated behavior in a manner [21] _____ the way in which they affect positively motivated behavior. It would be very desirable to have a drug that affected only one kind of behavior, for example, psychotic behavior. However, the likelihood of such specificity is small; in fact, the probability that a drug will affect only those behaviors that a particular society considers socially undesirable is indeed small.

[21] different from, other than, etc.

This brief overview is intended to whet your appetite for the more detailed presentation of CNS pharmacology that follows. To see whether you have met the objectives of this chapter, try the self-test. The items are so easy that you should get them all correct; later chapters will be more challenging.

SELF-TEST

A. Most drugs that are used therapeutically for their effects on the CNS do not cure the underlying CNS pathology. True or false? [1] _____

[1] True

B. A defining symptom in psychoneuroses is [2] _____

[2] anxiety

C. Is schizophrenia a neurotic or a psychotic disorder? [3] _____

[3] psychotic

D. Morphine is an example of a [4] _____ analgesic.

[4] strong

E. Drugs used to induce sleep or prepare a patient for sleep are called [5] _____.

[5] sedative hypnotics

F. The most widely used alcohol by humans is [6] _____ alcohol.

[6] ethyl

G. General anesthetics in gaseous form are administered by [7] _____.

[7] inhalation

H. A sensory experience that occurs in the absence of sensory stimulation is called a [8] _____.

[8] hallucination

I. The effects of a drug on behavior depend on the [9] _____ setting in which a drug is given, on the [10] _____ level of the drug that is administered, and on the rate and pattern of ongoing [11] _____ of the organism. This last determinant of a drug's effect on behavior has been called the law of [12] _____.

[9] environmental

[10] dose

[11] behavior

[12] initial value

J. Animal experiments do not provide strong support for the idea that drugs affect positively and negatively motivated behavior differently. True or false? [13] _____

[13] True

K. Aspirin is a [14]_____ analgesic. [14] mild

L. Heavy metals and pesticides have effects on the CNS. True or false?

[15]_____ [15] True

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2. GENERAL PRINCIPLES OF PHARMACOLOGY

This chapter is devoted to a brief discussion of some general principles of pharmacology. If you are using this text as part of a course in pharmacology, you probably already know this material in greater detail than what is presented in this chapter. Therefore, you may wish to proceed immediately to following chapters. If you are in doubt about your mastery of these principles, try the self-test to see if you already know the material.

For those of you who have not been exposed to the general principles of pharmacology, this chapter presents an overview of some of the more important pharmacologic concepts that apply to drugs in general. By the time you finish this chapter, you should be able to:

1. Describe the most important routes of drug administration and discuss how the blood levels change with different routes of administration.
2. Discuss some consequences of plasma binding, ionization, and blood-brain barrier permeability on the penetration of drugs into the brain.
3. Define some differences between graded and quantal dose-effect curves.
4. Define the following terms: agonist, antagonist, reversible antagonist, irreversible antagonist, additivity, potentiation, synergism, metabolic tolerance, and pharmacodynamic tolerance.

Before a drug can produce an effect on the CNS, the drug must enter the CNS. The entry of drugs into the CNS depends on the chemical and physical characteristics of the drug and the characteristics of the living organism to which the drug is administered. We will consider some relationships between these factors in this chapter.

The first factor to be considered is the route of drug administration. People usually take drugs by swallowing them; this is referred to as the *oral route* of administration. Although drugs may be partially absorbed through the mucosa of the mouth when taken

by the [1] _____ route, most of the absorption takes place farther down the gastrointestinal (GI) tract in the stomach and the intestines. The oral administration of drugs has an important advantage. Drugs can be swallowed easily and no special equipment is required. This permits many patients to take their drugs at home without direct medical supervision. Largely because of this advantage, drugs are given more frequently

[1] oral

by the [2] _____ route of administration than by any other route.

[2] oral

There are some disadvantages to the oral route. If, for example, the patient is not conscious, it is difficult to give drugs orally. Furthermore, drug absorption by the oral route may be too slow when rapid drug effects are needed. Absorption of the drug can be slowed even more if food is present in the stomach. Some drugs are so poorly absorbed from

the GI tract that it is useless to give them [3] _____ .

[3] orally, by the oral route

Some drugs given by the oral route do not reach the circulatory system until they have been changed chemically, or metabolized. Enzymes in the GI tract metabolize many drugs. Furthermore, the circulatory system of the body is arranged so that drugs absorbed from the intestine must pass through the liver before entering the general circulation.

Thus, many drugs when administered orally are [4] _____ in the liver before entering the general circulation. Therefore, the amount of unchanged drug that ends up in the general circulation after oral administration depends largely on the extent

[4] metabolized, chemically changed

of [5] _____ from the GI tract and the extent of metabolism in the liver.

[5] absorption

The liver is particularly important for the enzymatic [6] _____ of drugs. When a drug is metabolized in the liver, usually two things happen. First, the active drug is converted into an inactive form or a less active form (although a few drugs

[6] breakdown, metabolism, conversion to inactive forms, transformation

are converted to more active forms). Second, the drug becomes more polar; that is, it is chemically changed to a form that is more water-soluble. After the chemical conversion,

the [7] _____ form of the drug is excreted from the body more easily, as we shall see in greater detail later. These effects on a drug when it passes through the

[8] _____ are important because the pharmacologic effects of drugs are generally directly related to the amount of active drug in the circulation.

Another major route for administering drugs is by injection into the body with a syringe and needle; this is usually referred to as *parenteral administration*. Injection of a

drug into a vein or artery is the most rapid method of [9] _____ administration for distributing the drug throughout the body, because intravenous or intra-arterial injection places the drug directly into the circulation. After a rapid intravenous injection into the blood, the delivery of the drug to the brain depends largely on the circulation time of the blood. Because the brain has a relatively high blood flow, intravenous

injections bring drugs to the brain very [10] _____ .

Drugs also are frequently injected into muscle or under the skin; these are referred to as the *intramuscular* and *subcutaneous routes,* respectively. When the drug is injected into

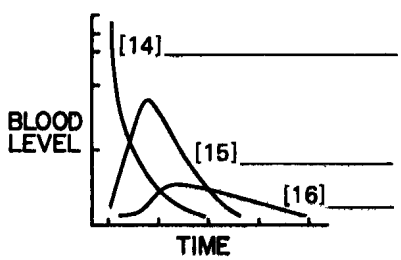
the tissue, it again must be absorbed into the [11] _____ to be carried to the brain. The rate of absorption depends on such factors as the solubility of the drug in the tissue fluids, the chemical and physical characteristics of the drug, and the blood flow through the tissue. Blood flow through muscle is greater than blood flow through the skin, so the absorption of a given drug administered by the intramuscular route usually

is [12] _____ than when it is subcutaneously administered.

Other routes of administration for drugs include the *rectal, intraperitoneal, sublingual, nasopharyngeal, spinal,* and *intradermal routes.* These routes are used much less frequently than those already discussed. One very important route of drug administration that is used to administer gaseous agents (e.g., general anesthetics) is administration

through the [13] _____ . We will be discussing this route in detail when we study general anesthetics.

The accompanying graph shows the blood levels of a drug as a function of time after its administration by intravenous, intramuscular, and oral routes. Can you label the three curves correctly?



Once a drug enters the blood, regardless of whether it was injected directly by the intravenous route or absorbed after administration by some other route, it still may not reach the CNS very easily. One of the reasons for this is that many drugs bind to tissues, particularly to plasma proteins such as albumin and globulins. Phenobarbital, for example,

[17] _____ to albumin. When a drug in the blood binds to

[18] _____ , the binding is usually reversible – which means that there is an equilibrium between the free drug (not bound to plasma proteins) and the fraction

of the drug that is [19] _____ to plasma proteins. The fraction of the

[7] polar, water-soluble

[8] liver

[9] parenteral

[10] rapidly

[11] circulation, blood, bloodstream

[12] faster

[13] lungs, respiratory system

[14] intravenous

[15] intramuscular

[16] oral

[17] binds

[18] albumin, plasma proteins

[19] bound

drug that is bound depends on both the nature of the chemical bond and the concentration of the drug in the plasma. This is important, because the drug when bound to

[20] _____ has great difficulty in crossing the capillary walls and leaving

[20] plasma proteins, albumin

the bloodstream. Thus, only the [21] _____ drug can enter the tissue (e.g., brain tissue). For the same reason that binding to albumin

[21] free, unbound

[22] _____ the entrance of drugs into the CNS, the filtration of the drug through the glomeruli of the kidney and hence its excretion are retarded. Further, most drugs are not subject to metabolism when bound to plasma proteins. Therefore,

[22] limits, slows, prevents

binding to plasma proteins is likely to [23] _____ the time the drug remains in the blood.

[23] prolong, increase

When the free drug crosses the capillary walls of the vessels within the CNS, it still may not be able to interact with neurons. The CNS consists of blood vessels, nerve cells, and glial cells. These glial cells in combination with the capillary walls constitute another barrier to drugs, particularly to polar drugs, which prevents them from reaching the neurons. This barrier is referred to as the *blood-brain barrier.* Many drugs that produce effects on the CNS when injected directly into the brain have no effect when given

systemically, because they do not cross the [24] _____ barrier.

[24] blood-brain

Another important factor that determines the extent to which a drug can enter nerve cells is the degree to which the drug ionizes. Many drugs that act on the CNS are weak acids or weak bases. As such, these drugs ionize in solutions such as body fluids. The fraction that is ionized is always in equilibrium with the fraction that is un-ionized, as shown below for a weak acid:

$$\underset{\text{Un-ionized Weak Acid}}{HA} \rightleftharpoons \underset{\text{Ionized Form}}{H^+ + A^-}$$

The membranes of cells appear to consist of a viscous lipid bilayer with globular protein partially embedded in it. The polar groups of both the lipids and proteins are on the surface of the membrane and the nonpolar groups are in the interior of the membrane. To enter a cell, the drug must cross this membrane. If the drug is ionized, it does not

cross the [25] _____ easily, because it is not lipid-soluble. A lipid-soluble drug – that is, a drug that is un-ionized – crosses the membrane more easily.

[25] membrane

Thus, a drug that crosses membranes easily will be lipid-[26] _____ or un-ionized, whereas drugs that do not penetrate membranes easily will be

[26] soluble

[27] insoluble

lipid-[27] _____ or [28] _____ .

The degree to which a particular drug is ionized depends on the physical chemistry of the drug and on the acid-base balance of the medium. Drugs that are weak acids, for example, become ionized in a basic medium and un-ionized in an acidic medium, whereas

[28] ionized

drugs that are weak bases are ionized in an acidic medium and [29] _____ in a basic medium. The degree of ionization affects not only the penetration of the drug into the cells but also the rate of excretion of the drug by the kidneys. In the kidney, most of the fluid that has been filtered from the blood into the tubular system is reabsorbed back into the circulation. Free drug filtered from the blood by the kidney will also be reabsorbed into the blood, depending on the drug concentration gradients between the tubular lumen of the kidney and the capillaries and on the extent to which the drug is ionized. Thus, a drug that is a weak acid will be reabsorbed to a greater extent in an

[29] un-ionized

[30] _____ urine than in a basic urine. A drug that is a weak base will

[30] acidic

be reabsorbed from the kidney to a greater extent in a(n) [31]_____ urine. One might increase the rate of excretion of an acidic drug by making the urine more [32]_____ . The metabolism of drugs to their ionized form hastens their [33]_____ by the kidney; however, the binding of drugs to plasma proteins [34]_____ their excretion, because drugs bound to proteins in plasma do not filter into the kidney tubules very easily.

[31] basic

[32] basic

[33] excretion

[34] slows, decreases

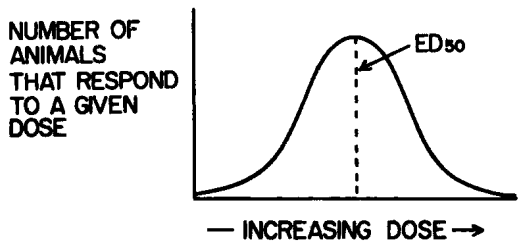
Although it seems almost too obvious to restate it, one of the fundamental determinants of a drug's effect on the CNS is the dose. Perhaps the most important contribution that pharmacology has made to science is the establishment of a fundamental relationship between the dose of a drug and its pharmacologic effect. The effects of a drug cannot be well described unless the effects of several doses have been determined. The functional relationship between the doses of a drug and its effects is called the *dose-effect curve.*

There are two basic kinds of dose-effect curves, called *quantal* and *graded* dose-effect curves. In the quantal dose-effect curve, the biologic system responds in an all-or-nothing fashion. The description of the lethal effects of a drug as a function of dose, for example, would be a [35]_____ dose-effect curve, because death is an all-or-nothing state. A graded dose-effect curve is used to describe a biologic system that can respond partially to a drug. The relationship of drug dosage to changes in the blood pressure, for example, is usually described by a [36]_____ dose-effect curve. In CNS pharmacology, graded dose-effect curves are used predominantly. Nevertheless, some time will be spent studying quantal dose-effect curves, because it is easier to develop concepts about dose-effect relationships from these curves.

[35] quantal

[36] graded

If we take a large number of animals and plot the number of animals requiring a given dose to produce a response versus increasing dose levels (as shown below), a quantal dose-effect curve takes the shape of a *normal distribution.*



Because the doses for quantal responses to drugs are usually distributed normally and are described by the bell-shaped [37]_____ curve, we can apply normal-distribution statistics (standard deviation, standard error, and so on) to quantal dose-effect curves. The *median effective dose,* which is the dose that produces a particular effect in 50 percent of the animals tested, is often derived from the dose-effect curve. Pharmacologists refer to this as the "effective dose, 50 percent" or the ED_{50}. If the response being measured is the lethality of the drug, the mediam effective dose is the "lethal dose, 50 percent" or LD_{50}. Although the ED_{50} and the LD_{50} describe only single points on the dose-effect curve, pharmacologists frequently use these points for comparing drug effects.

[37] normal, normal-distribution

Another important concept derived from quantal dose-effect curves is that of a *threshold dose,* which can be defined as the minimum dose that is required to produce a measurable effect. As shown in the normal-distribution curve above, half of the animals do not respond to the drug at the ED_{50}. For those not responding, the [38]_____

[38] threshold