BASIC PHARMACOLOGY IN MEDICINE

Joseph R. DiPalma

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Second Edition

Joseph R. DiPalma, M.D.

Editor
Professor of Pharmacology
Vice President and Dean
Hahnemann Medical College and Hospital, Philadelphia

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Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The editors and the publisher of this work have made every effort to ensure that the drug dosage schedules herein are accurate and in accord with the standards accepted at the time of publication. Readers are advised, however, to check the product information sheet included in the package of each drug they plan to administer to be certain that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in regard to new or infrequently used drugs.

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Department of Pharmacology
Hahnemann Medical College and Hospital
Philadelphia, Pennsylvania

Preface

In this the second edition we have tried to follow the format of the first edition. Students have been generally receptive to the first edition but certain deficiencies have become evident which we have attempted to correct. Obviously, the parent text, *Drill's Pharmacology in Medicine,* has become obsolete and cannot be used as a basis for ready reference in many subjects. As a result, some subjects not covered in the first edition have now been included in the second. Extensive revision and updating of all chapters have been undertaken to represent new knowledge and viewpoints.

This present edition as it has now been enlarged and revised stands as a text by itself. Consequently, we will no longer list the authors of individual chapters of the parent text. It would not be fair to these authors to attribute work to them which has been, in most instances, extensively changed. Yet our hope is that the present revision holds up to the standards which they so vigorously set.

This remains a short text designed primarily for student use. Conscientious students will supplement their education by reference to larger texts, but we have tried to include in this text the most significant body of information required for medical courses in pharmacology. We have continued to stress basic theoretical approaches in the first five chapters. The text also concentrates throughout on mechanisms of drug action as the requisite information for the initial course in pharmacology. Clinical pharmacological information such as pharmacokinetics and drug interactions has been included, thus preparing the student for more sophisticated therapeutic drug exercises in the clinical years.

Joseph R. DiPalma, Editor
Richard G. Sample, Editorial Coordinator

Preface to the First Edition

The faculty of the Department of Pharmacology at Hahnemann Medical College, from long experience in teaching a core curriculum using a number of major textbooks, has concluded that the medical student of today needs a book which is brief but also encourages exploration of each subject in depth. The purpose of the work would be to provide a concise presentation of the general theories and pertinent facts of pharmacology as they apply to medicine. To this end we have written this textbook as a companion volume to *Drill's Pharmacology in Medicine.* It has been abbreviated, edited, brought up to date, and simplified directly from the 4th edition of *Drill's Pharmacology.*

In the past two years we have written abbreviated chapters for our pharmacology course to supplement the major text. The enthusiasm of the students and the course's general overall success have encouraged us to undertake the task of an abbreviated textbook for the entire course in freshman medical school pharmacology. We believe we have learned how to handle the material so as to make it most useful to the student while still permitting the level of instruction to remain high.

It is quite evident that the present accretion of knowledge makes it impossible to compress all available information into the same number of hours which ten years ago sufficed. The question is what to include and what to delete. Our editors felt that all material on the nature and mechanisms of drug action which is reasonably established must be included. Certainly, a classical exposition of the major drug groups such as antibiotics, autonomic drugs, cardiovascular drugs, and central nervous system drugs could not be left out. However, many areas more peripheral to pharmacology, such as the vitamins and convulsive drugs, could be omitted. Toxicology of specific agents and less commonly used drugs, such as those for tropical diseases, can be taught in subsequent courses. Once the student has

mastered the major drugs, it should not be difficult to acquire information on other therapeutic agents by self-instruction.

The editors found that some sections of *Drill's Pharmacology in Medicine* could be included verbatim, and some sections had to be completely rewritten. All have undergone a critical process of reduction and reclassification. In all instances speculative and debatable material was eliminated. Many of the illustrations are from the major text. A bibliography, subdivided by chapter, appears at the end of the text.

The basic course in pharmacology must be one which can be built upon in subsequent courses in clinical medicine and applied basic science. The serious student can of course use the major text for a complete and exhaustive treatise. The minor text remains as a convenient summary of the basic facts he must know to go on to clinical medicine and to review for examinations. This method of study encourages self-instruction and provides the means for continuing education.

Editing this work has included many stages. A particular topic was initially prepared by one editor, then reviewed by a second group of editors (and usually torn apart). A rewriting in most instances made the grade. This was then subjected to review by graduate students in order to get a different and pertinent point of view. After these corrections and additions a final version was produced, which we consider to be direct, clear, and succinct.

For their very appreciable aid in the preparation of this text we wish to extend our sincere thanks to David M. Ritchie, Barbara T. Nagle, Robert J. Capetola, Emil Bobyock, and Margot Newman.

The Editors

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Part One

Modern Approaches to Pharmacology

Chapter 1

Measurement of Drug Action

As pharmacology entered its modern era at the turn of this century, it was realized that as a science it could not make any advances unless it dealt with the fundamentals of the relationship of the dose of a drug and the response of the organism. Quantitation of this relationship established certain useful principles which enabled pharmacologists and clinicians to better define drug action, compare active versus less active drugs in or out of a series, select appropriate doses for a specific desired response, define the limits of therapeutic and toxic effects, and in general establish the orderly study of drugs on a rational scientific basis.

As will be seen, the relationship between dose and response is an exceedingly complex one because a multitude of factors are involved—some known and some unknown, some controllable and some uncontrollable. In such cases only a logic which deals in a statistical methodology yields measurements which are meaningful and useful. Despite the complexity and the variability, it has proven to be possible to gather valid data which has very practical and relevant purposes.

COPING WITH VARIABILITY

To simplify the subject, in this chapter we make the assumption that a pharmacologic effect (or response) is produced when a drug in an "effective" concentration reaches a receptor site at a response or target tissue. Other variables and complications of the drug reaching this responsive site will be dealt with in subsequent chapters. A further assumption made is the elimination of time as a factor in the initial discussion. With these provisos the magnitude of response (maximum level from a single dose regardless of time) of an effective dose (and hence the plasma level) is determined by four general factors: (1) the affinity between the drug and the tissue receptors; (2) the intrinsic potential of the drug to cause cellular changes; (3) the responsiveness of the

target tissue at the time the cellular changes occur; and (4) the effectiveness of cellular and systemic reflexes in resisting or modifying the changes induced by the drug.

In disease, tissue responsiveness may be even more variable. The reflexes provoked by drug action are also in a dynamic state and are subject to considerable variations. Since the final outcome of drug action depends upon the interaction of all these factors and possibly others, it is apparent that it is necessary to cope with the problem of variability. Quantitative variability in pharmacology may be expressed in terms of either the *size of the effect* (intensity or duration) elicited by a standard quantity of a drug or the *size of the dose* needed to produce a standard response. Quantitative variability may be observed between individuals in a group of organisms or even within a single organism when it is examined repeatedly with the same drug and dose.

The underlying reasons for pharmacologic variability may be ascribed to two major causes: (1) the variation in the purity or composition of the drug preparation, and (2) the constantly changing physiologic and biochemical state of an organism.

The vast majority of drugs used in medicine are chemically pure and reasonably stable and therefore make only a minor contribution to pharmacologic variability. However, there is a relatively small number of drugs, mainly of biologic origin, with a significant potential for causing considerable variability in drug effects. This group includes drugs of unknown composition (such as some hormones) and drugs composed of mixtures of active ingredients in proportions that are not uniform (such as digitalis powder). The standardization of the potencies of insulin and digitalis powder are typical examples of the successful reduction of pharmacologic variability through biologic assay.

Most of the variation attending the use of drugs, especially in therapeutics, lies in the wide ranges of physiologic, biochemical, and pathologic conditions that confront the drug when it is administered to a living organism. The physiologic and biochemical states of an organism at systemic, tissue, cellular, and subcellular levels have a great influence on the final outcome by determining the pharmacokinetics of the drug. In this regard, age, sex, body weight, body surface area, basal metabolic rate, and other biologic characteristics of living organisms are all known to affect quantitatively the results of drug action. Moreover, the pathologic state of a subject can influence all the above conditions and, in addition, may even have a major role in determining the maximum extent of pharmacologic effect that can be obtained.

Age-related differences in drug activity require the proper application of pharmacokinetic principles (see Chap. 3). Both the therapeutic actions and adverse effects of pharmacologic agents may be different in neonates, infants, or older children than in adults. Age-dependent factors such as body compartment size, plasma protein binding, and levels of liver enzymes influence the basic pharmacokinetic phases of absorption, distribution, biotransformation, and excretion. For example, in infants as compared with adults the brain comprises a much larger proportion of the total body mass. In the geriatric patient, changes in life-style, possible increased sensitivity of target tissues, reductions in normal body functions, and changes in body weight and composition can alter the pharmacokinetic profile. The recently developed field of pharmacogenetics reveals yet another source contributing to pharmacologic variability. The genetic modification of pharmacologic responses can be attributed to receptor site abnormalities, drug metabolism disorders, tissue metabolism disorders, or anatomic abnormalities.

Dose-Response Relationships

The quantitative assessment of drug action is based on the principle that the magnitude of a drug effect is related to the dose administered. This fundamental principle, the dose-response relationship, is one of the most important in the science of pharmacology. There are two types of dose-response relationships, the *graded* type and the *quantal* type. In general four variables are represented in graded or quantal curves: time, biological unit, dose of drug administered, and the effect which is produced by the given quantity of drug.

Graded Dose-Response Curve The graded dose–response curve is defined as a quantitative curve in which increasing doses of a drug produce varying changes in effects when a single biological unit is employed. The single biological unit may be an intact organism (such as a human being), a piece of tissue, or even a single cell. An example of the

graded curve is given in Fig. 1-1. In this type of dose-response relationship the dose of drug and the effects are variables whereas time and the biological unit are held constant. When the dose of drug is gradually increased and the first noticeable effect is observed, the dose which produces this effect is referred to as the *threshold dose.* Further increments of drug administration result in larger effects, until additional amounts of drug cause a leveling off of the response at the *ceiling effect.*

In order to gain an informative display of the data, it is convenient to plot, not drug concentrations, but their logarithms on the abscissa. The resulting curve is sigmoid (S-shaped). If the doses were not plotted in logarithms, the curve would be a hyperbola and would offer less information than a sigmoid curve. This is so because the semilogarithmic curve spreads out the beginning of the hyperbola and thus shows more of the important low-dose range, the middle of the sigmoid curve is very nearly linear and therefore easily yields numerical parameters (slope and intercept), and the high-dose part of the dose-response curve is compressed by the logarithmic representation into a manageable size for the whole curve (Figs. 1-1 and 1-2). Therefore, the mathematical transformation of the dose units to logarithms is the conventional way in which the graded dose-response curve is presented.

Knowledge of the general shape of the graded curve for a given drug has practical use in medicine when a patient has to be virtually titrated with the drug in order for the optimum result to be achieved. Because the central part of the semilogarithmic graded curve is linear, the rate of change of response in that range is directly related to the rate of change of the logarithm of the dose.

Besides the linear portion of the curve, the minimum dose yielding the ceiling effect has some importance. This ceiling dose has served as the basis for a systematic comparison of the therapeutic efficacy of drugs. Also, the ceiling dose has a use in therapeutics where the aim often is the achievement of a maximum pharmacologic effect. In addition, doses exceeding the ceiling dose may actually provoke different and possibly undesirable responses.

Quantal Dose-Response Curve The quantal, or all-or-none, dose-response curve shows the relationship between the dose of a drug and the proportion

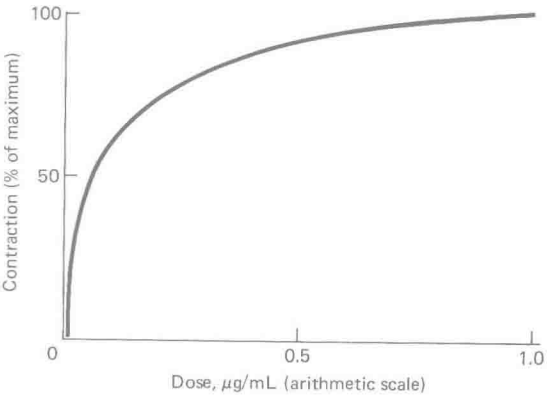

Figure 1-1 A graded response curve for increasing concentrations of a drug in a perfusion bath of a perfused isolated gut. Plotted on an arithmetic scale, the contraction response is hyperbolic as the concentration of the drug is increased until a ceiling effect is achieved.

of biological objects or units manifesting a specified pharmacologic effect. Thus in the quantal dose-response curve the doses and units are variables while the response and time are held constant. To examine the relationship between dose and quantal response it is necessary to use many units which are divided into groups, and then each group receives a certain dose of drug. The observed proportion (percentage) of the group responding to each dose with

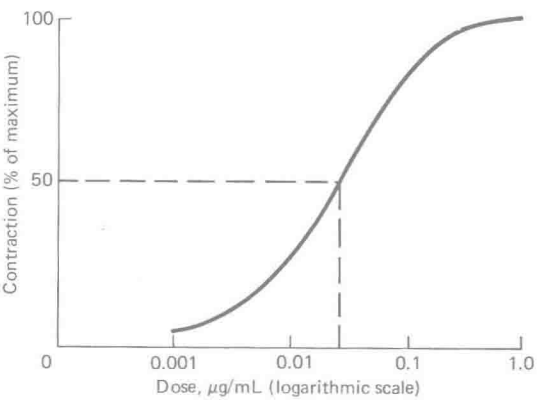

Figure 1-2 The same data as in Fig. 1-1 except that the dose is now plotted as a negative logarithm. The curve now becomes sigmoid in shape with a nearly linear central portion. This is far more convenient to interpret and has the advantage that the 50 percent maximal response may be easily determined. For these reasons the log-concentration curve has become the standard dose-response curve.

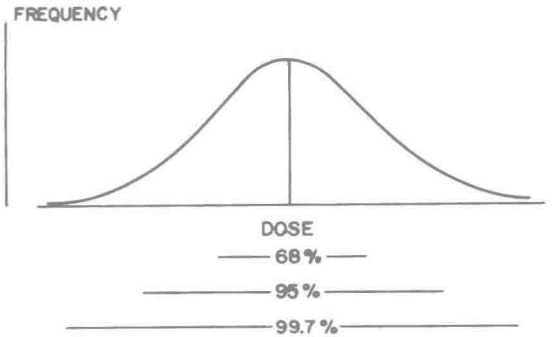

Figure 1-3 A graphic expression of the theoretical normal distribution of doses needed to elicit a quantal response in subjects from a large sample. The horizontal bars delineate the borders of ±one, two, and three standard deviations from the mean dose, which is shown by the vertical bar. The proportion of subjects requiring doses within the boundaries is indicated as a percentage of the sample. The dose units are unspecified.

the specified effect is determined. The pharmacologic response is assessed in the quantal dose–response relationship as an all-or-none response. For example, if a hypnotic drug is being tested in a group of individuals, only those individuals who are put to sleep by the drug have displayed the stated pharmacologic effect. The other individuals who are awake have not responded to that particular dose. Therefore, the percentage of frequency of response is calculated for that group.

In its most basic form the quantal dose–response curve takes the shape of a gaussian or normal distribution (Fig. 1-3). The gaussian distribution illustrates a simple random variation in doses needed to produce a response. Usually one obtains dose distributions that are imperfect normal distributions because the sample is too small, one or the other end of the distribution is not available (truncation), or some extraneous drug effect or other experimental limitation opposes or modifies the main action of the drug.

In a symmetric normal or bell-shaped curve, the value that has the greatest frequency is called the *mode;* it is equal to the *mean* (average value) and *median* (the value that bisects the population of values into equal halves). Furthermore, the two inflection points on the curve occur at values which are plus or minus (±) one standard deviation from the mean value and therefore enclose 68 percent of the values in the distribution. Because the bell-shaped curve is not a convenient form for the analysis of quantal dose–effect data, other graphic forms have been developed through mathematical transformation. Three of the graphic forms are illustrated in Fig. 1-4, which shows the data for two dose-response curves. It is common practice to obtain two quantal dose–response curves for a drug, one for the therapeutic response and one for some toxic manifestation. The data in Fig. 1-4 show the therapeutic effect and a toxic response from a drug in various groups of individuals.

The observed proportion (percentage) responding to the drug with either the therapeutic or toxic effect can be plotted against the dose of the drug, as shown in Fig. 1-4*a*. This is the form that the normal distribution curve (Fig. 1-2) assumes when the number of individuals responding is summed from the lowest to

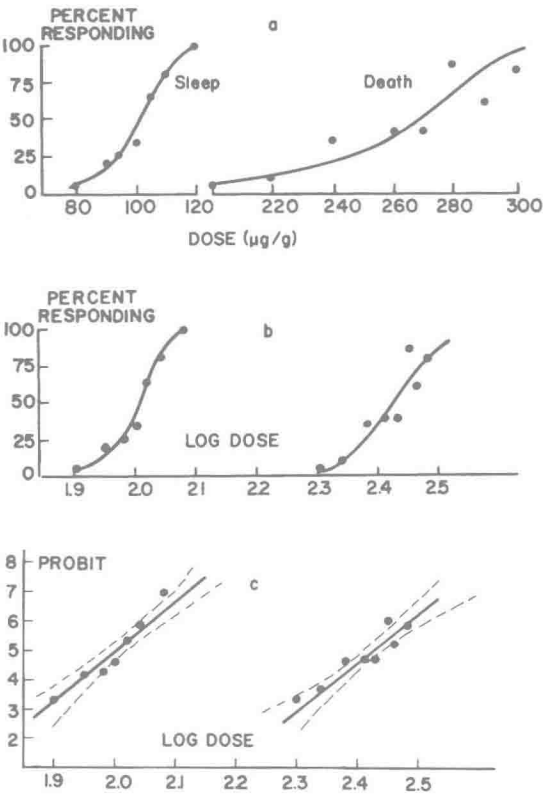

Figure 1-4 Three graphic forms, showing data for two dose-response curves. (See discussion in text.)

the highest doses. For example, the number of individuals who showed the desired response in each group studied is added. The number of individuals in group 1 who responded to the lowest dose is divided by the total number of individuals in the sample studied, and thus the percentage responding is determined. For the second dose of drug the number of individuals who exhibited the therapeutic effect are added to the number of individuals from group 1. This accumulated number is divided by the total number of individuals who responded in the study, and the total percentage responding to the second dose is obtained. This process continues until 100 percent is reached. The resulting sigmoid curve is referred to as a *cumulative* or *integrated normal curve.*

In Fig. 1-4*a*, the dose-response curve for the therapeutic effect is a reasonably good sigmoid curve, but the toxic-effect curve is not. This amount of variation is common when data on toxic or lethal effects are obtained. Many quantal curves often show a definite skewing in one end of the curve, usually the higher end. The skewing may be eliminated with an appropriate mathematical transformation of the dose unit. The one most often used is the logarithmic transformation in which the logarithm of the dose, rather than the dose itself, is plotted on the abscissa. Replotting the same data using log-dose improves the shape and the symmetry of the curves (Fig. 1-4*b*).

The extremes of the integrated normal curve, however, are nonlinear and approach the upper and lower limits of the response asymptotically. In order to make the quantal dose-response curves linear over a wider range of doses, the data can be replotted on coordinates in which the logarithm of the dose is plotted on the abscissa, and the corresponding number of standard deviations, rather than the percentage responding, is plotted on the ordinate. The mean of the curve (50 percent responding, or zero standard deviation) is assigned the value of 5, and each standard deviation, plus and minus, is numbered correspondingly.

This unit of response is termed *probit* (from the contraction of the phrase *probability unit*). The relationship of probits to cumulative percentage response is given in Table 1-1. Figure 1-4*c* shows this probit versus log-dose representation of the same information which was given in Fig. 1-4*a* as percent responding versus dose. It is seen that probit 5 corresponds to 50 percent responding. The group between probit 4 and probit 6 includes 68 percent of the individuals who have shown the given pharmacologic effect; between probit 3 and probit 7, another 27 percent. Thus, a linear plot is obtained representing 95 percent of the entire population studied.

Table 1-1 Probits Equivalent Deviates and Corresponding Percentage Values

Probit	Percent responding
8	99.9
7	97.7
6	84
5	50
4	16
3	2.3
2	0.1

The quantal curve, expressed in this manner, can be used to estimate, graphically, the mean dose, to determine the standard deviation of the doses about the means, and to determine whether a set of data follows a normal distribution. It also serves as the basis for biologic assays.

STATISTICS OF THE QUANTAL DOSE-RESPONSE CURVE

Arithmetic Mean Dose

The arithmetic mean (average) dose of a drug is the dose computed as the sum of all the doses required to produce a stated response, divided by the number of such doses in the summation $x = S(x)/N$.

The arithmetic mean has two important properties: the sum of all deviations from the mean is equal to zero, and the sum of the squares of these deviations (that is, error of estimation) is a minimum. These two properties make the arithmetic mean an *efficient* and *sufficient* statistic to describe the central tendency of drug doses.

Standard Deviation and Standard Error

The *standard deviation* shows the variation or scatter of individual values around the mean of all the