BASIC PHARMACOLOGY IN MEDICINE

JOSEPH R. DiPALMA, M.D.

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PREFACE

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

The Natural Laws Concerning the Use of Drugs in Man and Animals

The quantitative aspects of drug action constitute one of the principal fields of study in pharmacology, providing a basis for analytic investigation of the mechanisms of action and for a rational use of drugs in therapeutics.

A drug produces a pharmacologic effect when the concentration or quantity of the drug at the site of a responsive tissue attains some critical minimum level. The magnitude of this "effective" 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 of these factors, it is apparent that pharmacology is beset with an inordinate amount of quantitative variability. The following sections deal with the problem of pharmacologic variability and the methods used to cope with it.

THE NATURE, EXTENT, AND CAUSES OF PHARMACOLOGIC 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, 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 in the final outcome by determining the amount of drug that reaches the site of action, the rate at which it accumulates at that site, the rate and extent of biotransformation of the active drug to an inactive form, and the rate of elimination of the drug from the body. 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 of the above conditions and, in addition, may even have a major role in determining the maximum extent of pharmacologic effect that can be obtained.

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.

STATISTICS OF DRUG ADMINISTRATION

Conventional statistics such as the mean and standard deviations are basic statistics that can be used to describe the quantitative aspects of drug action.

Perhaps the most fundamental principle of pharmacology is that which states that the magnitude of a drug effect is a function of the dose administered. There are two basic types of dose-response relationships: (1) the *graded*, or *quantitative*, type which relates the dose of a drug to the size of the response in a single biologic unit; and (2) the *quantal*, or *all-or-none*, type in which the relationship is between the dose of the drug and the *proportion* of biologic objects displaying a given pharmacologic effect. The biologic material may be an intact organism, an isolated tissue, or even a single cell.

Dose-Response Curves (Graded)

An example of the graded curve is given in Fig. 1-1. As the dose administered to a single subject or to a discrete organ or tissue is increased, the pharmacologic response will increase in a gradual, smooth fashion, provided the dose has exceeded a critical level called the *threshold dose*.

The upper end of the curve has essentially the same properties as the lower end. The degree of effect produced by increasing doses of a drug will

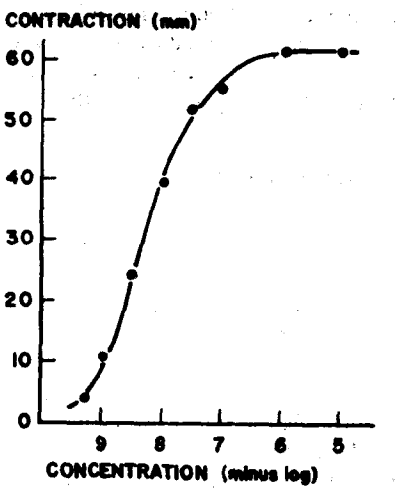

Figure 1-1 A graded response of an isolated aortic strip to increasing concentrations of norepinephrine. The isotonic contractions of the aorta are expressed in millimeters on the ordinate; the concentrations are shown on the abscissa as the negative values of the exponents of the concentrations; that is, $8 = -\log 10^{-8}$ g/ml.

eventually reach a steady level, the so-called "ceiling effect." Doses beyond the one that produced the ceiling effect, that is, the ceiling dose, do not elicit any further increase in effect. In fact, doses exceeding the ceiling dose may actually provoke different and possibly undesirable responses. In spite of this disadvantage of vagueness, the ceiling dose has a considerable importance in therapeutics where the aim often is the achievement of a maximum pharmacologic effect. It is interesting that the ceiling dose has served as the basis for a systematic comparison of the therapeutic "efficacy" of drugs.

The main body of the graded curve lies between the threshold dose and the ceiling dose. The graded curve may describe a symmetric sigmoid curve, an asymmetric sigmoid curve where either end may be distorted, or even one-half of a sigmoid curve (the upper half), which would then make it a hyperbolic function. 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. It is usual that the central part of the graded curve is linear for a range so that the rate of change of response is directly related to the rate of change of dose. Since a linear function of dose on effect offers convenience, the boundaries of linearity have been considerably extended by means of a mathematical transformation of the units of measure of either the dose, the response, or both.

Dose-Response Curves (Quantal)

The quantal, or all-or-none, curve relates the frequency with which any dose of a drug evokes a stated, fixed (all-or-none), pharmacologic response. It is therefore essentially a curve describing the distribution of minimum doses that produce a given effect in a population of biologic objects. Minimum (or threshold) doses for the effect can be obtained either directly by titrating the subject with the drug until the desired effect is produced or, alternatively, by giving a series of doses to different groups of subjects and noting the proportion of subjects responding to each dose. In either case, the frequency of occurrence of threshold doses can be plotted against the actual dose on any of several different coordinate systems.

In its most basic form, the quantal dose-response curve takes the shape of a gaussian or normal distribution (Fig. 1-2). The gaussian distribution suggests that the observed variation in doses needed to produce the response is due to simple random variation.

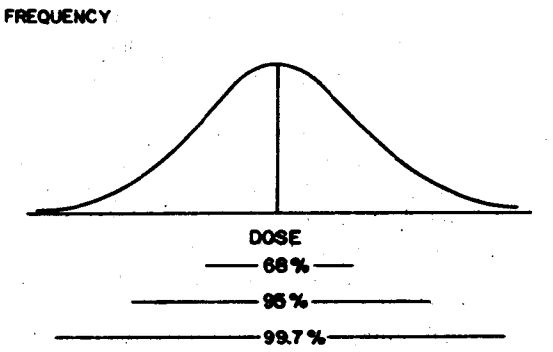

Figure 1-2 A graphic expression of the theoretical normal distribution of doses needed to elicit a quantal response in subjects from a large sample. The horizontal bars delineate the borders of ±1, 2, and 3 standard deviations from the mean dose, which is shown by the vertical bar. The proportion of subjects requiring doses within the boundaries is indicated as a percentage of the sample. The dose units are unspecified.

It is usual to obtain dose distributions that are imperfect normal distributions, either because one or the other end of the distribution is not available (truncation) or because some extraneous drug effect or other experimental limitation is opposing or modifying 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 ± 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. Three of the graphic forms are illustrated in Fig. 1-3, which shows the data for two dose-response curves.

Every drug has at least two quantal dose-response curves, one for the desired pharmacologic response and one for some unwanted toxic manifestation. The data in Fig. 1-3 were obtained by

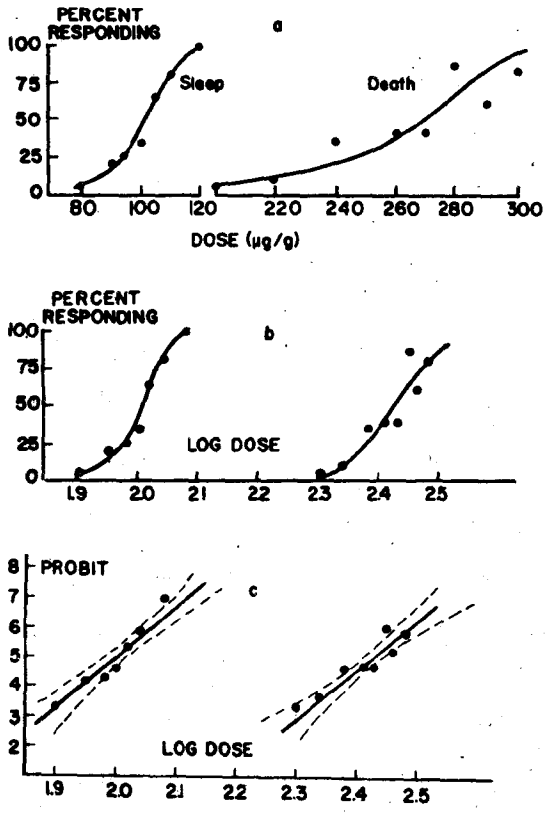

Figure 1-3 Three graphic forms, showing data for two dose-response curves. (See discussion in text.)

injecting groups of 20 mice with different doses of a central nervous system depressant, phenobarbital, and observing the presence or absence of the righting reflex. If the animals lost the righting reflex, they were regarded as being "asleep"; if they died within 24 h, the dose was considered lethal. This is an example of the indirect method for determining the individual threshold doses for the quantal responses sleep and death.

The observed proportion (percentage) responding to the drug with either sleep or death can be plotted against the dose of the drug, as in Fig. 1-3*a*. This is the form the normal curve shown in Fig. 1-2 takes when the number responding is integrated from the lowest to the highest doses; it is referred to as the *accumulated* or *integrated normal curve*. In Fig. 1-3*a*, the dose-response curve for sleep is a reasonably good sigmoid curve, but the lethal curve is not. This amount of variation is not uncommon in pharmacology when the end point (death in 24 h) is subject to an extraneous factor such as the development of bacterial infection as a sequel to prolonged central nervous system depression. Many quantal curves often show a definite skewing in one end of the curve, usually the higher end. The skew must first be corrected with an appropriate mathematical transformation of the dose unit (metameter). The one most often used is the logarithmic transformation in which the dose is simply converted to the log-dose.

Replotting the same data using the log-dose improves the shapes and the symmetry of the curves (Fig. 1-3*b*).

The extremes of the integrated normal curve, however, are usually nonlinear and in fact approach the upper and lower limits of response only 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 ordinate is expressed simply in multiples of the standard deviation called *normal equivalent deviates* (NED). Normal equivalent deviates and their corresponding percent response values are tabulated in Table 1-1.

The use of the NED as an expression of the percentage response in quantal dose-response curves was further refined by the elimination of the positive and negative signs by the expedient of adding 5 algebraically to each NED. This unit of response is termed *probit* (from the contraction of the phrase *probability unit*). The concepts of the NED and probit, which were developed independently, con-

Table 1-1 Normal Equivalent Deviates and Their Percentage Values and Probits

Normal equivalent deviates	% Responding	Probit
+3	99.9	8
+2	97.7	7
+1	84	6
0	50	5
−1	16	4
−2	2.3	3
−3	0.1	2

siderably facilitate statistical computations. The relationship of probits to NED and percentage response is also given in Table 1-1.

The advantage in the use of the probit is seen in Fig. 1-3*c*, where the same data as in Fig. 1-3*a* and *b* are plotted linearly over a wider range of log-doses.

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

Statistics Derived from 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 $\bar{x} = [S(x)]/N$.

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.

Median Dose The median dose is the smallest dose that is effective in 50 percent of individuals.

The median effective dose, expressed symbolically as ED_{50} for *effective dose, 50 percent*, is in common use in pharmacology because of several favorable properties: (1) The entire population of doses need not be known for its estimation because it is obtained simply by interpolation between two doses, one to which 50 percent of organisms respond and one which elicits more than a 50 percent response. (2) It is unaffected by extreme values and hence is stable even in a skewed distribution. (3) The ED_{50} readily allows for the expression of the phenomena of synergism and antagonism when the interaction of two drugs is studied (see Chap. 2). (4) The error associated with its estimation is smaller than the error of any other estimated dose of the quantal dose-response curve.

Confidence Limits Every statistic derived from experimental data is only an estimate of the "true" value of the statistic in a population of infinite size, and each estimate is associated with an error which is expressed generally as the standard error for the statistic. Another more meaningful way of indicating the precision of a statistic is through the use of confidence limits. These are boundaries which are expected to contain the "true" value of a statistic at some selected level of probability. To illustrate, when the 95 percent confidence limits are calculated for an ED_{50}, the assertion is made that the true ED_{50} for the drug in an infinite population of animals will be found within these limits with a probability of 95 percent and will lie outside these limits, by chance, only 5 times out of 100 repeated experiments.

The confidence limits for an ED_{50} of high precision will have a narrower range than will those for a less precise statistic at the same level of probability. But since confidence limits are a function of the standard error of the statistic, the limits can always be narrowed to give greater confidence by increasing the number of animals used in arriving at the statistic.

Therapeutic Index The therapeutic index of a drug is an approximate statement of the relative safety of the drug expressed as the ratio of the lethal or toxic dose to the therapeutic dose. The larger the ratio, the greater the relative safety.

It is not sufficient merely to state the therapeutic index in terms of "lethal dose" and "therapeutic dose" without specifically defining where on the quantal dose-response curves these doses occur. One could, for example, speak of the *minimum lethal dose* and the *minimum therapeutic dose* or the *maximum therapeutic dose* and the *maximum lethal dose*. Most often the therapeutic index is based on the estimates of the ED_{50} and the median lethal dose (LD_{50}) of a drug, for the reasons presented in the discussion of the properties of the median dose. But the use of the median effective and median lethal doses is not without disadvantage, since median doses tell nothing about the slopes of the dose-response curves for therapeutic and toxic effects.

One method suggested to overcome this deficiency uses the ED_{99} or ED_{95} for the desired drug effect and the LD_1 or even the $LD_{0.1}$ for the undesired effect. Using these levels of response, the