esses. But the resolution into simpler processes has been partial, not complete, and the relation of the isolated mechanisms studied to the organization of the whole has thus far defied analysis and thus stands as a challenge to the embryologists of the future.

Wilhelm Roux was once asked by Emperor Franz Josef, who made a visit to his laboratory, how he made discoveries in experimental embryology. Roux replied that the investigator "must have a question in his mind, and then look for an appropriate method to force an unequivocal answer to it." Investigators have made great progress toward compelling an answer to the question raised by Aristotle, but the complete answer to it will never be known until a new Aristotle frames an equally cogent question or set of questions regarding the organization of the whole. Embryos are notoriously resistant to threats of force, and the new Aristotle, like the old, will surely be someone who, like Roux, like Harrison and Spemann, like Holtfreter, understands the living whole embryo sufficiently to deal with it on its own terms. Embryos are creative artists, and, like other artists, they create form. The difficulties that face whoever tries to explain their success have their counterparts in those confronting anyone who tries to account in specific terms for the greatness of any work of art. Knowledge of the molecular constitution of his pigments does not suffice to explain the genius of Leonardo. In embryology as in art, appreciation is probably more effective than atomizing as an introductory approach to the understanding of the genesis of form.

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Relationship between Stimulus and Response

The "shape" of the problem serves to clarify the disparity between graded and quantal response.

S. Loewe

In all sciences concerned with excitable biological systems, the task of quantifying the relationship between the excitatory stimulus and the biological response is complicated by the differences in excitability among the individuals studied. This article (*1*) tries to analyze the problems arising from this complication. As an almost uniquely suited proving ground for the analysis, the field of pharmacology has been chosen. This field is entirely devoted to the study of a chain of events that begins with the pharmacological stimulus, called "dose" (*D*), and ends with the ultimate response to this stimulus, called "effect" (E).

The practical importance of the carriers of the pharmacological stimulus, the "drugs," has directed the efforts in this field toward an especially ambitious goal—namely, that of arriving ultimately at a single numerical expression of potency (*P*), the stimulatory strength inherent in a drug. The greater the effect *E* elicited by a certain dose *D*, the higher the potency, and the greater the dose required to elicit a certain effect, the lower the potency:

$$P = f(E/D)$$

Hence, the student of potency sets out to measure the quantitative relationship between *D* and *E*. Very soon, however, he finds himself at a parting of the ways where one fork is marked "graded-response," the other, "quantal response." The road signs as well as the guidebooks may suggest that the two roads offer him an equal chance. Whether or not this conclusion is correct only a reliable road map will tell. Only a view of the *Gestalt* of the problem (*2*) will provide precise information on how closely akin graded and quantal responses are and on what role either of them plays in determining the dose-effect relationship and potency.

In such an endeavor, one must dispense with all and any procedures of transformation ingeniously introduced for biostatistical purposes—for example, with the use of metameters such as log *D*, *E* probit, and logit. Any such metameter (*3*) is a mathematical function of the magnitude "as measured," a function "used in calculations" "because of its convenience" (the quotations are from Gaddum, *4*) as a means of converting curvilinear into rectilinear rela-

The author is on the staff of the department of pharmacology of the College of Medicine, University of Utah, Salt Lake City.

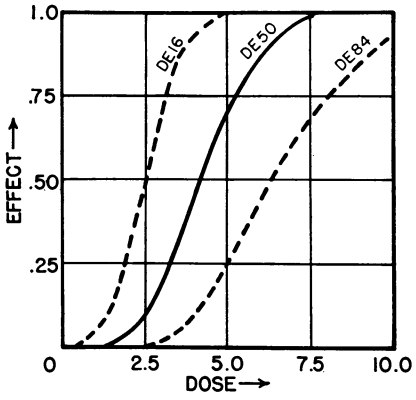

Fig. 1. Dose-effect curves. Curve *DE*50 is arbitrarily plotted on the basis of an assumed S-shaped course and of a tolerance value of 50. The two dashed curves for tolerance values of 16 and 84 were then calculated under the arbitrary assumption of constancy of the coefficient of variation at all levels of *E*.

tions (an instructive translation would be, "meta" equals "rubber," "meter" equals "band"). Whereas such orthopedic operations may excellently serve certain technical purposes, the faithful view, which I propose to display in this article, has to be drawn to scale and to depict the shape of the problem in all its natural curvaceousness.

Dose-Effect Curve

Customarily, the dose-effect relationship is graphically pictured in the form of the *D,E* curve which relates each dose *D* with its effect *E* in a diagram with the rectangularly intersecting coordinates of *D* and *E* (see the three arbitrarily plotted examples in Fig. 1). In all its simplicity, this form of presentation takes into account a number of noteworthy facts, such as (i) that the *D,E* relation is only a special case of stimulus-response relation, which again is a special case of cause-consequence relation; (ii) that *D* and *E* are continuously varying magnitudes; (iii) that *D* is the independent variable, whose conventional place is on the abscissa, and *E* the dependent variable, with its proper place on the ordinate. As to the yardstick of the two axes, *D* (the pharmacological stimulus) usually has the dimension of concentration (grams per kilogram; moles per liter, and so on) (*5*); the most general way of quantifying *E* (the change in physiological function) is to express it as a fraction of the maximal alteration of function that can be evoked by the optimally effective stimulus.

Variation of Tolerance

Though generally accepted, the concept of the *D,E* curve fits only the ideal case in which all individuals of the population of experimental subjects (organisms, tissues, cells, and so on) exhibit the same tolerance of the pharmacological stimulus. In reality, the individuals in any population differ in tolerance *T*. When large, randomly selected populations are tested in single-dose groups, the percentage of responders at any selected *E* level increases with the dose and, hence, can be taken as a measure of *T*. The value *n* of *T* for any particular D can be regarded as the tolerance of the *n*th individual in a population of 100 individuals arrayed in series of increasing tolerance (*6*).

Thus *T* enters the graphic view as a third variable whose axis is suitably presented horizontally at right angles to both a vertical *E* axis and a horizontal *D* axis. The result is a *D,T,E* space octant rising over a basal *D,T* plane. For every value of *T* there rises a vertical *D,E* plane containing a *D,E* curve of somewhat different course (compare the three curves, for *T*16, *T*50, and *T*84, plotted in Fig. 1). It is only in such a three-dimensional octant that the *D,E* relationship can be faithfully depicted. The real *D,E* relation is not shown by a single *D,E* curve but is represented by the integration of the *D,E* curves for all the different values of *T* into a *D,T,E* space surface. A model of the three-directionally curved surface, constructed from the values given in Fig. 1, is depicted in Fig. 2.

Isographic Views

For a more concise clarification of certain aspects of the spatial arrangement, the stereometric image can be reduced to two-dimensionality by way of parallel projections of suitable profile lines of the space structure upon the three border planes of the space octant. In the context of this study, only those two projection planes involving the vari-

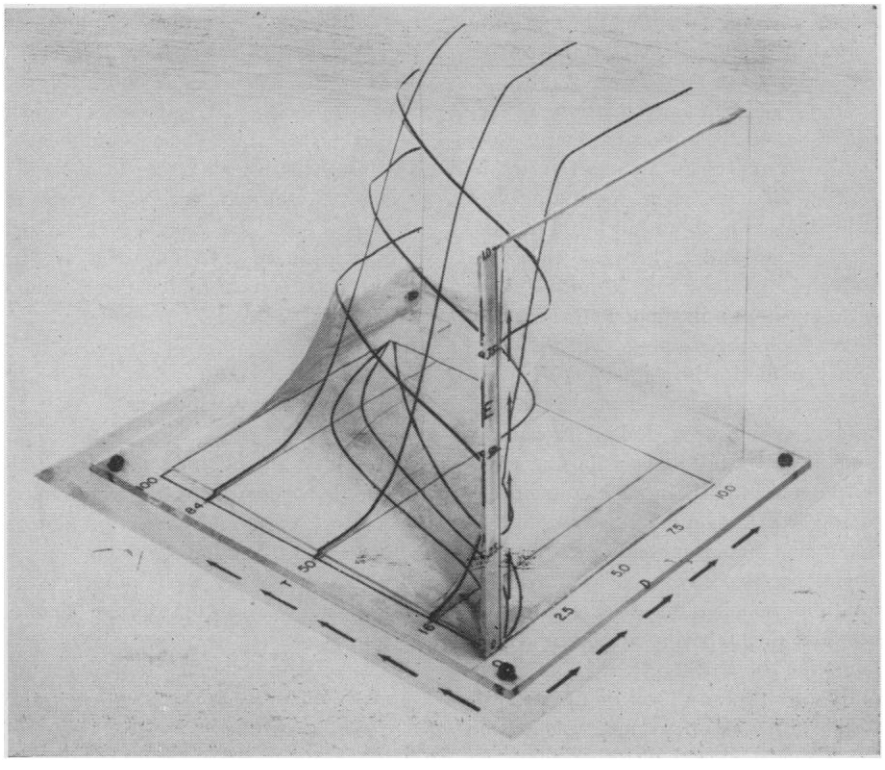

Fig. 2. Model of *D,T,E* space surface depicting the relationship between dose, tolerance, and effect. *D*, dose in values from 0 to 10 (mg/kg); *T*, tolerance in values from 0 to 100 (maximum tolerance); *E*, effect, marked in values of 0, 0.25, 0.5, 0.75, and 1.0 (maximum). The surface is constructed on the basis of the values employed in Fig. 1. The three curves rising with the slope of the space surface from its bottom to its top represent the dose-effect curves (isopleths) for tolerances 16, 50, and 84 respectively. Figure 1 shows their projections upon the vertical frontal border plane of the model. The three horizontal curves running from front to rear of the space surface represent the dose-tolerance curves (isobols) for effect levels 0.25, 0.50, and 0.75, respectively; their projections upon the basal *D,T* plane are visible in the lower half of this figure and also in Fig. 3. Note the complete disparity between the two types of curves.

able D are of interest—that is the vertical D,E and the horizontal D,T planes. In both planes the profile lines depict the relation between each two of the variables, the value of the third variable being constant along each curve and appearing only as its affix.

In an exhaustive projection picture, the profile lines would appear as an infinitely large family of curves—namely, of D,T curves and D,E curves, respectively. Discussion of such projection curves is facilitated by the general terminological usage designating them as *isograms* in reference to the third variable. Thus, the D,T, (E constant) curves in the D,T plane are designated by the term *isobol,* a word long employed (*7*) to name, in a map of any two variables, lines going through points of equal effect. No less appropriately, the term *isopleth* (taken over from geological maps where it is employed to designate lines going through points of equal content of an element) can be applied to any D,E,(T constant) curve in a D,E plane, along which the percentage of responders is equal.

It would be convenient if these still rather complex profile pictures could be further streamlined without loss of faithfulness in depicting the essentials of the respective D,T,E relationship. In the case of the isoplethic presentation of the D,E relation this is possible because the D,T curve represents a cumulative tolerance distribution where the majority of individuals is likely to fall in the middle range of tolerance, between two suitably chosen values $T < 50$ and $T > 50$, with maximum likelihood at $T50$. For this reason the isopleth for $T50$, together with the isopleths for $T16$ and $T84$ or any other two isopleths marking fiducial limits for a desired probability level, is quite apt to give a shorthand description of the essential characteristics of the D,T,E relation. (It may now be noted that Fig. 1 presents such a triple isoplethogram.) For obvious reasons, multiple isobolograms (see Fig. 3) do not lend themselves to a shorthand condensation of this type; the isobol for E 0.5, the midway level of E, lacks the focal statistical importance inherent in the $T50$ value, and no other short cut has yet been devised.

Floor Plans Supplement
Vertical Profile Plans

That all three variables, D, T, and E, must inevitably be taken into consideration in every dose-response problem is most clearly borne out by the procedural requirements arising when the picture of the general interdependency has to be replaced by the portrait of any individual case—that is, when the quantitative relations have to be expressed in concrete numbers. Even for a single D,E curve, of necessity isoplethic, the D value coordinated to a certain E value can accurately be established only by determination of the isobolic D,T curve at the desired E level. Accordingly, for a portrait of the three-dimensional D,T,E surface, a sufficient number of D,E isopleths for all pertinent T values and a sufficient number of D,T isobols at various E levels are equally prerequisite, the multiplicity of D,T isobols serving as the tool for establishing the T values of the D,E isopleths.

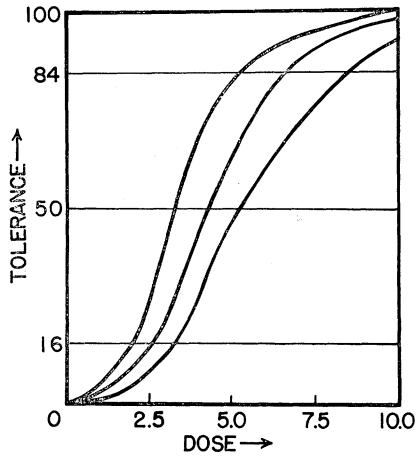

Fig. 3. Dose-tolerance curves at effect levels 0.25, 0.50, and 0.75, respectively, plotted on the basis of the data that underlie Figs. 1 and 2.

Spirit Level versus Altimeter

Now that a panoramic view of the relations between dose, effect, and tolerance has been unfolded, it is possible to allocate to "graded response" and "quantal response" their proper place and to arrive at a comparative characterization of their relations to D.

There is no doubt that the term *graded response* is synonymous with effect E, as defined for the purpose of the present analysis; the relation between dose and graded response is identical with the D,E relation envisaged in the preceding discussion.

The expression *quantal response* is not so self-explanatory. However, every description of the procedures employed in the study of quantal response makes it clear that first of all "a certain reaction" (*8*)—"some definite positive reaction" (*4*)—is selected and that specified doses are then given, each to several individuals, and the number of responders in each single-dose group is determined. The "certain reaction" employed as the touchstone of the individual's "all-or-none" response, if of any use for purposes of quantitation, must necessarily be of the nature of what is often called "endpoint" (of effect)—a term not referring to the upper "end" of the D,E curve but to any selected and quantitatively defined point on the D,E curve; it must signify a certain adequately constant level of E in the course of a D,E relation. (For the validity of this postulate it is irrelevant whether adequate definition of other E levels of this particular D,E relation is considered either negligible or technically impossible.) Thus, the relationship between dose and quantal response is identical with the D,T relation *at a certain fixed value of* E; the student of quantal response establishes *a single* D,T *isobol.*

Evidently the comparison between the objectives of graded-response and quantal-response studies reveals differences that lie deeper than merely in the field of procedure.

1) Judicious studies of graded response accurately evaluate altitude and slope all along the D,T,E surface. Determinations of quantal response yield numerical information on the tolerance distribution at a certain arbitrarily or involuntarily fixed elevation of that surface. If a more pictorial comparison is permissible, the student of graded response tackles the steepest *ascent* of the D,T,E surface, whereas the student of quantal response moves somewhere at the slope of the surface on a strictly *level* path.

2) Quite contrary to E, the value of T is determined solely by the biological subject. At constant T, E is unilaterally dependent on D; at constant E, the D,T relation describes the mutual interdependency of two independent variables. Thus, the role played by the respective two variables is essentially different in the dose-graded-response and the dose-quantal-response relation.

3) That the two phenomena, graded response and quantal response, are designated by the word *response* is not based on an essential similarity but on a merely incidental homonymity. In graded response, as in its customary use in physiology, the noun (correctly employed as a singular) is a term from the language of measuring; in quantal response it is a term from the language of counting (and would probably more correctly be

employed as a plural). The two meanings of *response,* one might add, are as unrelated as those of the word *freedom* in "freedom (meaning exemption) from thought" and in "freedom (meaning liberty) of thought."

Thus, from all aspects one arrives at the conclusion that graded response and quantal response are by no means essentially equivalent and that they are not mutually interchangeable approaches to the determination of the *D,E* relation. The single isobol, which is all that can be established by a quantal response, depicts the *D,T* relation at one (and only one) level of *E* and gives no information whatever on the *D,E* relation. Whereas a plurality of *D,T* isobols from different *E* levels serves as a tool in determining the *D,E* relationship, due regard being given to the variation of *T,* a solitary *D,T* isobol signifies, so to speak, only one out of many necessary manipulations with this tool.

Potency, a "Many-Headed Multitude"

Since the ratio D/E is a major determinant of potency, a broader view of the *D,E* relationship is liable to throw more light on the problems of potency as well. Neither *D,E* nor *D,T* curves can be expected to be rectilinear, nor can the *D,T,E* structure be a (mathematically) regular surface. Hence, "the potency of a drug" is *never a singular.* Even for the same quality of effect, potency varies with *E* as well as with *T*. A satisfactory image of the potency of a drug is as composite and as pluridimensional as the image of the *D,E* relationship. No formula is yet available by which this infinite multitude of potency values can be compressed into a single figure.

Whenever the potency of a drug is presented in the form of a single value, this signifies that the value is valid only for a narrow section of the large field of varying potencies and has been obtained by keeping some determinant variables constant and thus disregarding them. In this way, for instance, quantal-response procedure unassumingly pin-points its attention on establishing a value $1/P$ called "*ED*50." In this expression, "50" indicates that the $1/P$ value offered is valid only for *T*50—that is, for subjects exhibiting the median tolerance of the "normal" or "probit 5" individual. *E* in "*ED*50" is usually said to stand for "effective"; the meaning is clearer if it is interpreted as standing for "endpoint" —namely, for the particular level of *E* on which the isobolic *D,T* relation of the quantal-response study takes its course.

Fortunately, as discussed above, a quantal-response study, in order to arrive at the *ED*50 value by biostatistical interpolation, must first establish a number of *D* values for other tolerances in the course of the *D,T* isobol and can thus increase, though still only on the same constant *E* level, the amount of information considerably by adding data on the "error" (error due to the variation of *T*)—for example, the *ED*16 and *ED*84 values. These fiducial limits are often determined by admirably intricate biostatistical calculations; however, such intricacy must not mislead one into believing that the *ED*50 marks more than a single point on the *D,T,E* surface, that the *P* value derived from it marks more than one out of many different *P* values of the drug, or that the three *ED* values presented yield more than a still rather crude estimate of the tolerance distribution on the one particular *E* level. Nor must it divert attention from the fact that not even a much more exhaustively established *D,T* curve could give any information on potencies at other *E* levels. It is not necessary to emphasize that all these fallacies are avoided when the aforementioned graded-response studies of the real *D,E* relations, aided by studies of *D,T* relations at several *E* levels, are employed as the basis of multiple $1/P$ and *P* determinations.

References and Notes

1. This study was supported by a research grant (B-381) from the National Institutes of Neurological Diseases and Blindness, National Institutes of Health, U.S. Public Health Service.
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3. L. Hogben, as quoted in A. L. Bacharach, M. E. Coates, T. R. Middleton, *Biochem. J.* 36, 407 (1942).
4. J. H. Gaddum, *Pharmacol. Revs.* 5, 87 (1953).
5. If some biostatisticians and even biologists tend to attribute to dose the dimension of weight, they forget what the derivation of the word (Greek: *dosis,* a giving) implies—namely, that the weight of the drug powder does not per se constitute a stimulus but only "in dependency on circumstances of person and organ" [E. von Weizsaecker, in Bethe's *Handbuch der Physiologie* (Berlin, 1926), vol. 11, p. 14],—that is, in appropriate contact with the excitable substrate.
6. The term *tolerance* is employed here in preference to the closely related term *threshold.* Both are reciprocal functions of sensitivity; however, tolerance can be characterized as referring to the step from negative to positive response at any of a wide range of *E* levels, whereas the word *threshold* may be understood to refer only to the doorsill between lack of any response and the minimal perceptible *E* level.
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News of Science

AAAS Library Program Releases Book List: Elementary-School Traveling Library Launched

The AAAS Library Program, with support from the National Science Foundation, has this year issued a new catalog, *The AAAS Science Book List,* containing 900 titles. The new 140-page publication is a guide to recreational and collateral reading and to basic reference works in the sciences and mathematics for junior and senior high-school students, college undergraduates, and nonspecialist adults. It also serves as an acquisition guide for school and public libraries. The list has been prepared specifically as an aid in purchasing books (other than textbooks for class use) under the provisions of Title III of the National Defense Education Act of 1958.

Initially, United States book publishers provided complimentary copies of books on a preliminary list, which was then circulated for review and evaluation to members of the AAAS Council. Not only have all of the books listed been suggested by specialists, but, to assure their suitability, they have been read and evaluated by senior high-school students and college undergraduates already well grounded in the various fields of science and mathematics.

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