of the nucleic acid component and of polymers with many properties of proteins (*2*), is consistent with a unified concept of the origin of biochemical pathways in a predominantly phosphoric medium (*14*).

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3 February 1961

Quantal and Graded Analysis of Dosage-Effect Relations

Abstract. Loewe's recommendations regarding treatment of stimulus-response relations are criticized. Conditions are described where quantal analysis is justified. Loewe's interpretation of his graded analysis must be modified in the light of the fact that response curves for individuals frequently cross. Superior lines of attack on the problem are suggested.

Loewe (*1*) has examined the logical consequences of an investigator's decision whether to treat responses to drugs as graded (ordinally scaled) or quantal (dichotomized). He concluded that the two analyses bring out different relationships, and that since the chief concern in most experiments is to determine the relation of response strength to stimulus strength, the quantal analysis is inappropriate. Especially because the conclusion, if valid, would apply widely in behavioral and biological research, it requires close scrutiny.

Loewe regards as unsatisfactory analyses which discard an appreciable amount of important information from the data, and this view is beyond dispute. Two situations, however, may be distinguished: either differences in response strength all along the scale are important to the investigator (as Loewe assumes), or there is some response level E_0 of special significance, such that attaining it or not attaining it is far more important than differences in response level elsewhere on the scale. The second case is not infrequently encountered. In personnel selection a dichotomous criterion of job performance appropriately represents utility to the firm, if differences between satisfactory men and those who must be discharged are far more critical than differences in output among the satisfactory men (*2*). In a tryout of advertising, the consumer's decision to buy or not to buy the product should sometimes be studied without taking into account degrees of interest in the product above or below this point. Surely there are drugs (for example, anesthetics, insecticides) where a certain level of response marks the transition from useless to useful effect. There may be theoretical as well as utilitarian reasons for preferring to quantize data; Estes (*3*) argues for analyzing learning in terms of the appearance or nonappearance of a response rather than in terms of a scaled measure such as latency.

If there is a critically important E_0, the information desired is the proportion of subjects giving a response equal to or greater than E_0, as a function of stimulus strength (dosage, D, in Loewe's case). There may be more than one critical E; if so, more than one probability function can be plotted.

Even if gradations of response are important, Loewe's recommendations require re-examination. His mathematical model consists of a surface representing effect E as a monotone increasing function of dosage D and individual tolerance T. In the model, T is not clearly defined; we know only that the individual's responsiveness is expressed as a percentile relative to others under study. To summarize the surface conveniently, Loewe would use D,E cross sections (T constant at 50, 16, and 84, or other such values). Loewe then describes an experiment whose data are coordinated with this model. The proposed single-dose experiment consists of drawing random samples and giving to each sample a different dosage. This produces a distribution of E for each D, which can be converted into a curve representing cumulative probability p_E as a function of E. The curves for various D form a surface. Loewe identifies p_E with T, though one is a group statistic and one is a constant associated with the individual; hence he identifies the D,E,p_E surface with the D,E,T model. He takes cross sections with p_E constant as the desired summary curves.

Loewe's model appears to be overly restrictive. His surface represents actual data only if all individuals having a certain tolerance T have the same D,E curve, within the limits of experimental error. This can occur only if the set of curves for all individuals is disjoint, that is, if no two curves cross each other within the range of D under study. When curves are disjoint, the only fault in his recommendation is that he preserves too little information to satisfy the person for whom some E_0 is of prime importance.

As a matter of fact, however, learning curves, drug-response curves, and so forth, for individuals often cross (*4*, *5*). Some measure of the individual (for example, strength of response at some arbitrarily chosen dose) may be used to represent T, but for every T there will be numerous D,E functions, and a distribution of E against D, not a curve, will be obtained. Only when curves are disjoint is it correct to identify p_E with T. A single-dose experiment does not permit a test of disjunction. If such an experiment is performed, and if utility considerations make gradations of response important, Loewe's analysis is an acceptable method of summarizing the distribution of E as a function of D even though it probably does not represent the relation of E to D for constant T.

Wherever the risk of unwanted order effects can be disregarded, it is much more informative to carry out an individuals-times-levels experiment in which several points on the curve for each individual are determined by successive dosings. If the data support the assumed disjunction of curves, one can give Loewe's analysis the strong interpretation he proposes. If they do not, a more powerful analysis should be sought. One possibility is to divide persons into groups such that the set of curves within any group is disjoint, after which Loewe's analysis can be applied. Even more powerful is the technique of establishing a limited number of prototype curves and describing each individual's record in terms of one curve or a combination of them (*5*). Such techniques for recognizing individual variation in shape of curve as well as differences in threshold level are still in an early stage of development.

Loewe's argument is consistent only if we accept his hidden assumptions: that no level of effect is especially important, that D,E curves for individuals are disjoint, and that a single-dose ex-

periment is to be used. If curves intersect, as is likely, neither his experimental design nor his analysis is powerful enough to depict "without loss of faithfulness . . . the essentials of the . . . D,T,E relationship." As a step in the direction of taking individual differences into account, it is a useful procedure when interpreted somewhat differently than Loewe suggests. His case for rejecting quantization as a matter of principle does not appear to be well founded.

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27 January 1961

As is clearly stated in the introduction of my paper (*1*), the sole purpose was to examine the general question whether or not the task of quantifying the relation between dose (D) and effect (E)—which is appropriately solved by presenting the change in E with increasing D in a so-called "graded-response" D,E curve—can also be solved by presenting, in a so-called "quantal-response" curve, the change, with increasing D, of a third magnitude (called T in my paper, p_E in Cronbach and Gleser's), the percentage of test individuals attaining or exceeding a certain single preset E level (*2*). The question was answered—to the negative—by linking the three magnitudes concerned in a three-dimensional coordinate system with an E coordinate rising over a rectangular D,T plane, by then forming a D,T,E space surface under use of values freely chosen but compatible with experience, and by demonstrating that, since any quantal D,T curve lies in a horizontal, any graded D,E curve in a vertical plane, they intersect rectangularly "and never the twain shall coincide."

This simple demonstration of the nature of the relation between three basic magnitudes required no experiments, and in fact my paper contains no experimental data nor does it describe, prescribe, recommend, or touch any practical, technical, methodical, or procedural matter. From the fact that in Cronbach and Gleser's reply this model demonstration is called an "experiment" one may consider it possible that the authors have misunderstood the scope and essence of my article. It is food for such supposition that one encounters nowhere in their reply direct and specified objections against my completely theoretical demonstration or against conclusions drawn from it, or against both, but that instead their discussion begins with the extensive description of an "experiment" allegedly encountered in my paper ("Loewe then describes an experiment . . ."), the details of which then form the starting-points and targets of their objections. Even if it were appropriate to call my demonstration an experiment, the experiment described by Cronbach and Gleser is in many important respects unrelated to the object of my demonstration; it is *their* experiment, not mine.

It is true that my D,T,E model, by definition (and an extensive, unmistakable definition) is identical with what they call their D,E,p_E surface—which makes any objection to my "T" a mere quarrel about *names*. However, their experiment also deals with entirely new relations such as the enigmatic "p_E as a function of E." Most, and the most grave and intricate, objections are directed against the "single-dose experiment" character of "my" experiment. This obviously refers to the use of figures and curves obtained from single individual test objects rather than from groups of such. And indeed, actually all of the subsequent discussion of Cronbach and Gleser's reply is focused to the inadequacies, dangers, and fallacies of such "single-dose experiments." Now quite incidentally, although any such questions of experimental procedure are irrelevant in our analysis of basic relations, a technical subject was touched, quite at random, *once* in my article: by mentioning in reference to the D,T curves that the percentile distribution values are customarily (and, of course, necessarily) "derived from single-dose *group* experiments." And just as customarily in this statistically minded age the values for D,E curves come from single-dose *group* experiments. The authors' "anti-individual" campaign cannot possibly be due to misinterpreting "single-dose group" into its contrary; at any rate, such a campaign is directed to the wrong address, so much more so as in pharmacology intra-individual variation from one test to the other is a well-known, much discussed, and well-heeded phenomenon (see, for example, *3*). Unfortunately, both the constructive suggestion made by Cronbach and Gleser and their promise to contribute to future developments refer only to problems of individual variation, important in *their* experiment but irrelevant to my analysis of fundamentals and my two conclusions submitted: (i) that in the treatment of the problem in question, namely, how to obtain information on intensity of E as a function of D, the quantal-response D,T curve cannot replace the graded-response D,E curve, and (ii) that multiple D,T curves offer an important tool for statistically supporting and refining the graded-response information.

It is a distressing paradox that, in the summarizing sentence of Cronbach and Gleser's reply, this championing of mine for an appropriate application of quantal-response studies in graded-response investigations is called Loewe's "case for rejecting quantization as a matter of principle."

For those who still adhere to the belief that a quantal-response curve is equivalent to a graded-response curve in depicting the D,E relation, my image of the level path of the student of the former and the up-hill climb of that of the latter should perhaps be thrown into somewhat bolder relief: In college towns, such a strictly level promenade built halfway up along a hillside for the convenience of elderly scholars is often named "Philosophers' Lane"; should the meditating philosopher insist that in walking there he gained altitude, one would call that an illusion.

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Chromosomes of Lemurine Lemurs

Abstract. A wide variation in chromosome number and morphology was observed among different species and subspecies of lemurine lemurs. Comparative karyotype analysis indicates close phylogenic relationships and strongly suggests that chromosome structural rearrangements may have played an important role in the evolution of this group of primates.

The lemurs, a unique group of the most primitive primates, the Prosimiae, have survived millions of years. Their distribution has been limited to the island of Madagascar (the Malagasy Republic), and they are now threatened with extinction. Although the diversity of forms has been noted since before