A THEME ON VARIATION

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The old adage "variety is the spice of life" is a familiar one and those of us who work in the field of biological science enjoy the spice and, at the same time, acknowledge the variety in our statistical approach to biological phenomena.

Earlier this year I attended meetings of two professional groups - each of which was wrestling with essentially the same problem, but each from a different point of view. The problem was a scientific one or, more precisely, a biological one and the more I thought about it the more fascinating the problem became. Indeed, as I will try to show in what follows - some very fundamental questions are raised in connection with our scientific methodology and these have important implications to medicine.

At one of these meetings, which was concerned with drug toxicity, a paper was presented dealing with the predictive value of toxicity tests. As all those who have been exposed to pharmacology know, toxicity is expressed in the classical manner as the LD_{50}, i.e. that amount of a drug which will kill 50% of the animals to which it is administered. Since society frowns upon human experiments in connection with toxicity tests, such tests are performed on animals and the data obtained are extrapolated to humans. Thus, one may obtain a calculated LD_{50} for man, and in doing so, one recognizes that there may be considerable variation in the lethal dose for man because of a factor known as population variation or difference in sensntivity.

The person presenting the paper was making an argument for the observation that, in choosing or using an effective dose for one of his patients, the physician might feel a great deal more comfortable about administering a new drug if he knew the LD_1, rather than the LD_{50}. After all, there might or might not be a considerable spread between these two values. By convention, it is usual to compare the LD_{50} with the ED_{50} to obtain a measure of safety with which a drug may be used, but this procedure does not allow for those situations where there may be "overlap" of the effective dose curve and the lethal dose curve. The author concluded his remarks with a plea for routine LD_1 determinations in connection with new drug submissions. I could not help reflecting that what the physician really wanted to know was whether Mr. Smith was going to develop a toxic reaction from the effective dose he was preparing to give him.

The second meeting found physicians and lawyers discussing the use of "the breathalyzer" test as a means for judging the degree of the impairment of an automobile operator. The "breathalyzer" is designed to measure the concentration of alcohol in the expired air which, in turn, is a measure of the blood alcohol provided certain technical precautions are observed. Data obtained from thousands of analyses indicate that a person becomes impaired when the blood level of alcohol reaches a little over 100 mg per cent and certainly when it attains 150 mg percent. These data have been submitted to the most rigorous statistical examination so that one knows the standard deviations and the standard errors of these mean values. The fact that it is possible to quote such figures admits of population variation in sensitivity to alcohol and the lawyer is the first to recognize the limitations of such values. To him, it is useful to know that Mr. Smith's blood level falls within the range of values accepted as indicating impairment, but, he realizes that this is no more than stating that "Mr. Smith was probably impaired". In many cases, this is not good enough, for the lawyer really wants to know "Is Mr. Smith in fact impaired?"

The lawyer's problem, you see, is not very different from that of the physician who is about to use a new drug on his patient. Both are asking questions about specific individuals and the only answer available to them in each case is a statement of probability. Probability deals with populations, not individuals, and as a result both the physi-

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cian and the lawyer find little satisfaction in such abstractions. Neither of them are ever called upon to deal with populations.

One might ask at this point, how we as scientists and physicians ever got ourselves into this apparent impasse. Have we not been using sound methods of analysis and deduction?

Before answering this question, let us turn our attention briefly to the chemist or the physicist, who through his observations, has been able to deduce many of the so-called "laws of nature". These laws have become so firmly fixed in our minds that we have probably overlooked their real nature. The physicist and the chemist, by and large, work with matter in its various forms and therefore are dealing ultimately with the behavior of molecules and atoms. Since each deals with astronomically large numbers of molecules at one time (there are 6 followed by 23 zeros molecules in 3 1/2 teaspoons of water), the "law" or truth that deiives from the analysis appears to be much more "accurate" than the truths that the biologist uncovers; and small wonder for, were we able to establish an LD_{50} on 6 million, million, million, million white mice, our standard errors might also be vanishingly small. But think of housing, injecting and disposing of all those animals, or even of paying for them if some animal farm were able to provide them!

The physical scientist is seldom plagued by the shortcomings of his analytical methods which, by and large, are not very different from those of a biologist, for a very simple reason — he does not deal with individuals. His analyses tell him what to expect in the way of behavior of populations of molecules; and since he is always dealing with large numbers of "experimental objects", his data are ideally suited to his purpose. He will be quick to admit that his results tell him nothing meaningful about the behavior of an individual molecule, except that there is a certain probability that it will react in a certain manner or occupy a certain position in space.

We, in the biological field, are constantly faced with the problem of population variation and are, therefore, forced to design our experiments so that account may be taken of this factor. Up to this point, we have dealt with our world in much the same way that the physical scientist deals with his. But now we go one step farther, and attempt to apply this knowledge derived from a population study to predict the behavior of an individual - like Mr. Smith. It is not surprising that we run into difficulties! And when our predictions turn out to be right, rather than patting oneself on the back one should thank one's lucky stars that Mr. Smith turned out to be an "average individual"

It must be fairly obvious at this point that, if we require specific information about an individual, we must study the individual; and perhaps this is the only way out of the physician's dilemma. As far as the development of biological or medical knowledge is concerned, populations must be studied first. The results of these studies permit us to draw general conclusions regarding the behavior of man as a population of animals. Directly we wish to know something about Mr. Smith, then we must concentrate on Mr. Smith, particularly to find out whether he deviates from the "average individual". This, after all, is exactly what the physician does when he makes a routine examination of the patient.

When the question of toxic reactions to a drug arises, the same type of procedure might be followed, but the usefulness of such an examination to the predicting of toxic reactions necessitates the knowledge of how the toxic reactions to the particular drug arise. For instance, if a plasma cholinesterase test were performed on a patient, it would be very easy to predict whether this patient would develop a toxic reaction to procaine, or any other drug containing an ester link in its molecular structure. It follows, therefore, that predictive tests of this type require precise knowledge regarding the absorption, fate and excretion of a drug. From this information, the reaction associated with toxicity might be singled out and simple tests designed to measure the particular reaction. Thus, when Mr. Smith presents signs and symptoms that require the use of Diabolicol the physician would consult his handbook and find that he should request an ortho-methyltransferase test plus an estimation of inulin clearance. Simple? Yes, but time-consuming.

At this particular stage in the development of our knowledge, the above suggestion is little more than a pious hope; but it is far from being an impossibility. Until we reach this ideal state, it is well to remember that variety can be both the spice and the price of life, and we shall have to continue taking chances as far as the latter is concerned.