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INDIVIDUAL VARIATION IN RESPONSE TO DRUGS*

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Every practitioner is familiar with the wide variation shown by patients in their response to drugs. Therapeutic success is indeed dependent on the adjustment of standard methods and doses to the needs and peculiarities of the individual patient. Such work makes special demands on clinical skill and experience, and here the general practitioner has a special advantage on account of his knowledge of the patient's peculiarities. It is sometimes suggested that medical practice is degenerating into an automatic process whereby diagnosis is supplied by a laboratory and the appropriate remedy by a therapeutic index. The individual variation of patients will, however, always constitute a factor limiting such tendencies, and is a sure safeguard against the replacement of practitioners of medicine by automatic machines.

The actual range of individual variation tends to be ignored because most therapeutic methods are such that the amount of drug given can be adjusted to the individual need. If the same dose of a drug is given to every individual in a large population then the extent of individual variation is at once revealed. Therapeutic methods of this type, however, are comparatively rare.

The usual method adopted in the administration of powerful drugs is to start with a small dose and to observe the effects produced on the patient before working up to a full dose. The administration of a volatile anaesthetic is an example of the manner in which it is usual to correct individual variation, since the anaesthetist concentrates his attention on each patient, and by suitable adjustment of the dosage secures a uniform response. Most well-established clinical methods of drug administration are of this type, and hence the range of individual variation is masked, and indeed is in danger of being forgotten. This is evidenced by the fact that from time to time therapeutic methods are recommended which involve giving patients a full dose of some potent drug without providing any opportunity for first determining their individual response to it. In most cases such a risk is unnecessary, but in some it is very desirable to produce a full therapeutic action as quickly as possible, and therefore to know the probable limits of human variation. The chief problem is to ascertain what ratio between the average lethal dose and the therapeutic dose represents a reasonable margin of safety in the use of a drug. The extent of the margin actually desirable is a matter of opinion, but it will be generally agreed that if a therapeutic measure involves the chance of

producing a serious toxic effect even in one case in 1,000, it must be considered dangerous. This chance will therefore be taken as representing the limit of justifiable risks.

The determination of the incidence of severe toxic effects is obviously a problem which the clinician is glad to leave to the laboratory worker, and hence no apology is needed for the discussion of evidence provided by animal experiments. In order to measure directly the occurrence of occasional toxic actions it is necessary to use very large populations; considerations of cost preclude the employment of any but small animals, and therefore the discussion of individual variation must be based chiefly on experiments made on large numbers of rats and mice. It is obvious that there is a very wide difference between mice and men; but for the reasons mentioned the evidence available is limited, and it is necessary to make as much use as possible of the existing material.

Individual Variation in Animal Populations

The lethal dose of a drug is a primary pharmacological constant, and usually is one of the first characteristics to be determined. Until about twenty years ago the method employed was to give varying doses to a dozen or a few dozen animals, and to term the smallest dose which produced death the minimum lethal dose. Such doses were stated as mg./kg., and thus correction was made for variations in body weight. The introduction of the biological standardization of drugs necessitated increased accuracy in such methods, and as soon as systematic investigations were made it was found that animals showed a considerable individual variation in their responses to drugs, and that consequently the methods that had been in use for a century were inherently inaccurate.

The outstanding results of research of this type are as follows. All populations of animals show individual variation to all drugs. The extent of the scatter of the individual variation depends both on the nature of the population and on the drug. The scatter can be reduced by making the population as uniform as possible—for instance, by the use of inbred animals instead of stock animals, and by the use of animals similar in sex, body weight, and age. The nature of the diet is another important factor—for example, vitamin deficiency increases the susceptibility of animals to many drugs (Wien, 1936). Finally, it is essential to use only animals in good health. Even when all of these precautions are taken animals still show a wide variation in their response to drugs. For example, Poe, Suchy, and Witt (1936) measured the lethal dose of strychnine salts for rats. They used about 4,000

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animals, and therefore their results are statistically significant. In the case of adult male rats the average or mean lethal dose (50 per cent. mortality) was 2.25 mg./kg., but 4 per cent. were killed by 1.5 mg./kg., and a similar number survived 3.5 mg./kg. They found, moreover, that the mean lethal dose for adult females was 60 per cent. of that for males, whilst the mean lethal dose for young animals was about 70 per cent. that for adult animals. In the case, therefore, of adult animals of mixed sexes 4 per cent. were killed by about one-fourth the dose which 4 per cent. survived. In view of this result it is not surprising to note that previous workers who had estimated the minimum lethal dose for strychnine on rats by the old method of using one or two dozen animals had obtained results varying from 0.7 to 3.4 mg./kg.

The scatter shown in the individual variation of the response to drugs unfortunately differs very widely in the case of different substances. The simplest method of describing the scatter is by measuring the coefficient of variation. The "standard deviation" in the response to a drug is approximately equal to the difference between the doses producing 50 per cent. mortality (mean lethal dose) and that producing 16 per cent. mortality. (For the sake of brevity the mean lethal dose will be termed M.L.D.) The difference between these two doses expressed as the percentage of the M.L.D. is approximately equal to the "coefficient of variation." Examination of characteristic curves which relate dosage and percentage of mortality show that these vary from steep symmetrical sigmoid curves to highly skewed curves approximating in form to a hyperbola. The coefficient of variation in the former case may be as low as 10 per cent., whilst in the latter case it may be as much as 50 per cent. The occurrence of curves of the latter type raises the following difficulty. Our aim is to discover what percentage of the M.L.D. is likely to be safe—that is, to kill less than one animal in 1,000. The determination of this fact by direct experiment would involve the use of at least 10,000 animals for a single drug; but if the shape of the characteristic curve from 10 per cent. to 90 per cent. mortality is established, and the laws of probability can be applied, then it is possible by extrapolation to calculate the chance of a mortality of 1 in 1,000. If a variation is due to a large number of independent factors of similar importance then the distribution follows the "normal curve of error"; and if, for example, 90 per cent. of the M.L.D. kills 16 per cent., then the standard deviation (σ) is $100 - 90 = 10$, and $100 - 3\sigma = 100 - 30 = 70$ per cent. of the M.L.D. will kill about one individual in 1,000.

This simple calculation cannot, however, be applied to highly skewed curves, since it produces the absurd result that a considerable proportion of a population is killed by a dose of less than nothing. It has been shown by Gaddum (1933) that reasonable results can be obtained if characteristic curves are plotted with the dosage on the logarithmic scale. This converts the skewed curves described above into sigmoid curves. In the case already mentioned a 16 per cent. mortality is produced by nine-tenths of the M.L.D., and according to this method of estimation 1 in 1,000 mortality would be produced by $(9/10)^3 = 73$ per cent. of the M.L.D. In this case the two methods of calculation give very similar results, but in a case where 16 per cent. mortality is produced by half the M.L.D. the usual method of calculation results in the absurd conclusion that 3 per cent. mortality is produced when the dose is *nil*, whereas the logarithmic method gives the possible result that 1 in 1,000 mortality is produced by $100 \times (\frac{1}{2})^3 = 12.5$ per cent. of the M.L.D.

The calculation of incidence of effects by plotting the factor causing the effect on a logarithmic scale is not a new suggestion, since its use was recommended and justified in the case of living populations by Galton and MacAlister as long ago as 1879. Table I gives a few

TABLE I

	Fraction of Mean Dose which should Produce Effect	
	Once in 1,000 Individuals	Once in 10,000 Individuals
Lethal actions :		
Digitalis on frogs	0.5	0.42
Neoarsphenamine on rats	0.56	0.5
Strychnine on rats	0.47	0.4
Thallium on rats.. ..	0.47	0.39
Amytal on cats	0.5	0.42
Dysentery toxin on rats.. ..	0.036	0.016
Insulin convulsions in mice	0.33	0.25

typical results obtained with this method of calculation. These results show that although individual variation always occurs, yet, with carefully selected populations of rats, its range in the case of many important drugs is relatively narrow, and that in most of the cases quoted a dose equal to 40 per cent. of the M.L.D. is safe (that is, will not kill more than 1 in 10,000 individuals). The example of dysentery toxin proves, however, that certain poisons are inherently unsafe, since the individual variation is so great that a very small fraction of the mean lethal dose will suffice to kill susceptible individuals.

The drugs that are shown by animal experiments to be possibly safe are obviously of chief interest, and the problem is to estimate what proportion of the mean lethal human dose is safe therapeutically.

Human Lethal Dose

We are at once confronted with the difficulty that the mean lethal human dose is not known for any drug. In the case of a common poison such as strychnine textbooks of toxicology provide the following information. Several deaths have occurred when the dose taken was probably not more than 1/2 grain. Deaths from 1/4 grain have been reported, but the evidence is less certain. Recovery after 2 grains is fairly well established, and recovery after 3 or 4 grains has been reported. Obviously it is nearly always difficult, after the occurrence of a fatal case of poisoning, to obtain reliable information as to what dose has been taken. Furthermore, in the case of recovery it is always uncertain how much of the drug has been removed unabsorbed from the stomach. It is worth noting, however, that animal experiments with strychnine proved that there was a fourfold range of dosage between the least resistant and the most resistant 5 per cent. of a population, even when every endeavour had been made to exclude causes of variation. Hence there is no reason to suspect the statement that some adults have been killed with 1/2 grain of strychnine and others have recovered from 2 grains.

The animal experiments are of service in that they provide formal proof of the fact that the minimum lethal dose is a quantity which cannot be measured accurately. It is simply the smallest dose that has been observed to be followed by death, and in the case of any drug the greater the population observed the lower the value is likely to be.

It is therefore preferable in toxicology to describe the usually fatal dose, and to avoid the term minimum lethal dose.

Human Variation to Narcotics

Quantitative evidence regarding the extent of the variation of the response of patients to therapeutic doses of drugs is very scanty. In the case of the narcotics used for pre-anaesthetic medication a certain amount of accurate evidence exists, because drugs such as nembutal, sodium amylal, and evipan are given by slow intravenous injection until a constant response is produced. Such methods provide exceptionally accurate evidence regarding the relation between dosage and the incidence of a constant response in a human population. For example, Paxson (1932) measured the amount of sodium amylal (mg./kg.) needed to produce analgesia in fifty-five women during labour. His results show that 16 per cent. were narcotized by three-fourths of the median narcotic dose. This is a variation like that found for the lethal action of sodium amylal in cats, rabbits, and rats (Swanson and Page, 1927), and for the related compound sodium nembutal given intravenously to dogs and rats (Swanson and Shonle, 1931) and to rats alone (Gage, 1933). Variations of a similar extent were observed in these cases in respect to both the hypnotic and the lethal doses.

Similarly in the case of avertin given per rectum, the figures of Flörcken and Mues (1928) indicate that 50 per cent. of the population is narcotized by 80 per cent. of the dose needed to narcotize 84 per cent. The scatter as regards the proportion of a population of rats anaesthetized by graded doses of avertin (per rectum) is of similar extent (Lendle, 1928; Tunger, 1931; Gage, 1933). These facts permit the calculation of the extremes of response that are likely to be encountered in a population of 1,000. These are shown in Table II.

TABLE II

Ratio of Doses Producing Effect in 16 and 50% of Population (D_{16}/D_{50})	Percentage of Mean Dose (D_{50}) Producing Effect		Ratio a/b
	(a) In 0.1% Population	(b) In 99.9% Population	
0.75	42	237	1/5.6
0.8	51	200	1/3.9
0.9	73	137	1/1.9

Reports regarding the occurrence of exceptional responses to basal narcotics indicate variation within the scale shown in Table II. In the case of avertin Shipway (1936) found that 1,300 out of 1,500 cases were narcotized by doses between 0.09 and 0.1 g./kg., but that three cases (0.2 per cent.) required 0.12 g./kg. This distribution suggests a ratio D_{16}/D_{50} of a little less than 0.9.

In the case of evipan McNelis (1936) noted that in 1,000 cases one man required 4 grammes to produce anaesthesia, and that with one woman 0.9 gramme appeared to be an overdose. This is the type of result to be expected from a D_{16}/D_{50} ratio of 0.8.

These results indicate that the variation in human beings in response to narcotics is very similar to the variation which occurs in animal populations. It would appear that a D_{16}/D_{50} ratio of about 0.8 must be expected, and consequently in a thousand cases it is probable that the most resistant individual will require about four times the dose needed by the least resistant individual. This unavoidable and unpredictable human variation would seem to consti-

tute an important limiting factor in basal narcosis. Those methods in which the dosage can be adjusted to the individual response would appear to be preferable to those in which a standard dose has to be given to all patients. The latter method is satisfactory in the majority of cases, but produces unfortunate results when individuals are encountered who represent the extreme of variation.

Blood Alcohol and Intoxication

The measurement of the concentration of alcohol in the blood seems to be a much more accurate and scientific method than the estimation of the degree of intoxication by clinical examination. It is important to note, however, that although the former method may indicate accurately the amount of alcohol that has been taken, it does not indicate the effect produced on the patient, because there is a wide individual variation in regard to alcohol concentration in the blood and intoxication. This is shown by the reports of Bogen (1927) and of Widmark (1932), which describe in 250 and 562 cases respectively both the blood concentration of alcohol and the result of clinical examination. The results agree in demonstrating that a concentration of alcohol in the blood of 1.2 mg. per 100 c.cm. produces intoxication in 50 per cent. of cases. Bogen's figures show that intoxication was not present in any case in which the alcoholic content was less than 1 mg. per 100 c.cm.; whilst Widmark found none below 0.8 mg. per 100 c.cm., but observed six cases of intoxication in thirty individuals in whom the blood concentration was between 0.8 and 1.0 mg. per 100 c.cm. At the other end of the scale Bogen's figures show one case in thirty-five not intoxicated with 4 to 5 mg. per 100 c.cm., whilst Widmark's figures give one case in twenty-nine not intoxicated by 2.5 mg. per 100 c.cm. The ratio between the alcohol concentration not intoxicating the most resistant individuals and that affecting the least resistant individuals was about fourteen to one in Bogen's series and three to one in Widmark's series.

Examination of the figures shows that they do not follow the ordinary laws of probability, for there appears to be a lower limit of about 0.8 mg. per 100 c.cm., below which intoxication never occurs; whilst a concentration of 1.2 mg. per 100 c.cm. produces intoxication in about 50 per cent. of the population, but the more resistant half of the population reveals a wide scatter.

Animal experiments give a relatively small variation in response to alcohol. For example, Lendle's (1928) figures suggest a D_{16}/D_{50} ratio of 0.9. The difference in the results obtained with men and with rats is easily explained on the assumption that there is little natural variation with regard to the effects of blood alcohol on cerebral functions, but that a certain proportion of the human population acquire tolerance. Incidentally the results obtained by Bogen and Widmark provide fairly clear proof that the variation in tolerance to alcohol, which is such a familiar fact, is not merely due to differences in the rate of absorption, but that in addition there is a considerable individual variation in the effect produced by alcohol in the blood on the functions of the brain.

Measurements of the relation between the quantity of alcohol drunk and the incidence of intoxication would probably show a much wider scatter of individual variation than do the figures under discussion, because of wide differences in the rate of absorption of alcohol from the alimentary canal. Bogen's figures disclose a wider scatter of variation in the resistant half of the population than do Widmark's figures, but even in the case of the latter the distribution indicates that one individual in 1,000

would not be intoxicated by about four times the blood alcohol concentration that intoxicates 50 per cent. of the population.

Massive Digitalis Therapy

Digitalis preparations are standardized biologically on cats and on frogs, and figures for the variation in response of large populations are available. These figures show a very uniform response. The ratio D_{16}/D_{50} is about 0.9, and hence a dose equal to 73 per cent. of the mean lethal dose would kill only one individual in 1,000. Such results suggest that massive digitalis therapy may be a relatively safe procedure. There is, however, a very wide difference between a population of healthy cats and a population of patients with heart disease of varying intensity. Animal experiments prove that this apparent uniformity in response is obtained only when acute toxic effects are observed. For example, Bauer (1933) gave cats one-half a lethal dose of digitoxin, and then measured the amount of ouabain required to produce death twenty-four or forty-eight hours later. The individual variation with this latter dose was far greater than that found for the acute lethal action of these drugs. The ratio D_{16}/D_{50} was about 0.75, which indicates that one animal in 1,000 would be killed by 42 per cent. of the M.L.D. Similarly Li and van Dyke (1936) measured the individual variation in respect of cumulative poisoning in frogs. They gave doses of digitalis glucosides on alternate days, and their figures reveal a wide variation in the sum of the doses needed to produce death. The ratio D_{16}/D_{50} is about 0.4, and in this case a mortality of 1 in 1,000 would probably be produced by 1/16 of the M.L.D. Even with healthy animals, therefore, the uniformity of response to digitalis glucosides ceases as soon as opportunity is allowed for the action produced to be influenced by such factors as rate of excretion, etc.

The variability of the response of patients to digitalis therapy is well known; the following quantitative data give an indication of the scatter that occurs.

Murray Lyon and Gilchrist (1927) measured the changes produced in the heart rate by massive digitalis therapy. Their results show that the reduction in heart rate in cases of auricular fibrillation may range from 20 to 100 beats per minute, and that the greater the initial rate the greater was the reduction. In their group of thirty-seven cases with an initial heart rate between 70 and 100 per minute the reduction varied from 18 to 45 per minute in fibrillating cases, and from 0 to 40 per minute in non-fibrillating cases. Alstead (1936) noted the daily dose of powdered digitalis that produced nausea in thirty-six patients. In two nausea was brought about by 1 grain daily in a week, whilst in twenty-two cases 2 grains daily did not produce nausea in two weeks. Figures such as these indicate a wide individual variation in the response of patients to digitalis. The scatter of the variation appears to resemble the scatter observed in cumulative experiments on animals much more closely than the relatively uniform responses met with when the acute lethal dose of digitalis for animals is measured.

The question of practical interest is the probable margin of safety in massive digitalis therapy. The existing evidence is admittedly imperfect, but it suggests that in different individuals there is likely to be at least a fourfold range in the quantity of a drug required to produce a given effect. Consequently it appears to be very improbable that any method will be found of judging *a priori* the dose needed accurately enough to ensure that the average therapeutic dose will not produce severe overdosage in the occasional patient who is abnormally sensitive.

Conclusion

Individual variation is an unattractive subject because its existence constitutes a limitation to therapeutic measures of an annoying and irrational character. If a therapeutic method has produced satisfactory results in a dozen cases it seems irrational that the same technique should have an undesirable effect in the next case on which it is tried. It seems probable that the extent of individual variation is consistently under-estimated, because if an individual representing an extreme of variation happens to be encountered in a small group the result is apt to be discounted as an accident. The evidence available suggests, however, that whenever it is possible to measure quantitatively the effects produced by a drug in a large population an orderly distribution of variation in response is revealed. If this is the case, then the laws of probability indicate that if very large populations are studied occasional individuals will show very wide deviations from the mean response. These exceptional individuals are undoubtedly a nuisance from the clinical standpoint, but their existence must be recognized.

I feel that an apology is needed for the incomplete and inconclusive nature of the evidence collected in this paper. The examples chosen were the best I could find, and the result is evidence of the urgent need for fuller information regarding the distribution of human variation in response to drugs.

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The Hon. Edward Cadogan, deputy chairman of the National Advisory Council set up by the Government to assist in the "National Fitness" scheme, gave an address recently at Harrogate in which he discussed the question of grants for projects of physical training and recreation. He said that when some local body was in need of funds for building a club, gymnasium, or swimming pool, or to lay out a recreation ground, its proposals would go before an area committee, which, after examination, would pass them on with comments to the Central Grants Committee in London. Grants would not be given to central organizations for distribution, but would be made directly in aid of particular local projects put forward by the voluntary organizations and by local authorities. In the Government's efforts to make a healthier and a fitter nation the element of compulsion would be entirely lacking. Mr. Cadogan ended with a tribute to local authorities and voluntary organizations for having done so much with meagre resources to supply the needs of those over school age; but the demand for means for physical training and recreation now far exceeded the supply.