as cyanide. Flury and Zernik (p. 99) state that in the case of irritant gases the product $ct$ ($t$ = time till lethal action) is a constant, although as they point out, this is only occasionally true in the case of the gases with a general action.

The toxicity of an irritant gas for an animal can therefore be easily expressed quantitatively by the formula $ct = \text{constant}$. The susceptibility of different animals for different gases varies widely, and hence only experiments made on the same species of animal can be directly compared.

**Discussion.** Time-concentration curves can be fairly easily obtained with toxic gases, and the results form the only practicable basis for the comparison of the relative toxicity of these substances.

In the case of irritant gases the curves follow the very simple formula $ct = \text{constant}$, and hence are easy to compare.

In the case of gases with general toxic action the curves approximate to the formula $c^n t = \text{constant}$. If the results are plotted on a logarithmic basis it is easy to obtain a measure of comparative toxicity, provided the slope of the curves (i.e. the value of $n$) is similar.

If the value of $n$ is markedly dissimilar it is impossible to state any comparative measure of toxicity because the ratio of toxicity will differ with every time chosen. In many cases the action of gases with a general toxic action approximates to the formula $ct = \text{constant}$. The number of factors influencing the action must be very large and this provides another example of the fact that in the case of biological systems very complex relationships may often produce curves which can be fitted approximately by very simple formulae.

**Chapter 14**

**Individual Variation of Response to Drugs.**

**Methods of Measurement of Individual Variation.** One of the most familiar facts in medical practice is that no two persons respond in exactly the same manner to drugs. The use of biological methods for standardising drugs has necessitated the measurement of the extent and distribution of this individual variation in response to drugs, and in consequence a large literature has accumulated. Estimations of the distribution of individual variation of populations in respect of response to drugs are based on characteristic curves, which relate the dosage or concentration of a drug with the percentage of a population showing some selected response. The response which is usually chosen is death, but any other response can be used, provided that it permits the division of the population into two classes, those responding and those which fail to respond. In some cases the individual variation in response to drugs is distributed according to the normal curve of error, but in many cases skew distributions occur which cover very wide ranges of concentration.

An attempt will be made in this chapter to analyse some of the possible causes for this remarkable variety in the distribution of variation. The characteristic curves expressing distribution of variation are derived from various types of experiment.

(1) The most complete evidence is when the dosage required to produce an effect is determined for each individual in a large group of animals. In this case every individual response is known. The slow intravenous injection of tincture of digitalis into cats is a method of standardisation in which the exact dose needed to produce death can be measured for each individual. Lind van Wijn-
Methods of Measurement of Individual Variation.

Gaaarden (1924)\(^1\) measured the lethal dose in 573 cats and his results showed a symmetrical bell shaped distribution of variation. They ranged from \(-42\) to \(+56\) p.c. of the mean dose, and the standard deviation (\(\sigma\)) was about 12 p.c. of the median. These results require no discussion since the variation was measured directly in each individual, moreover the distribution of variation is symmetrical, follows the normal curve of error and shows a small scatter.

(2) In most cases however it is not possible to ascertain the dose needed by each individual, and hence it is necessary to use the group method. The population is divided into a series of groups and all members of a single group are given the same dose of drug. The percentage mortality for each of a series of doses is thus determined and the relation between dosage and incidence of death thus determined is termed a characteristic curve.

Fig. 53 shows the response of a population of rats to a series of doses of neoarsphenamine. In this case the standard deviation is 20 p.c. of the median. It will be seen that a frequency polygon can be integrated to form a characteristic curve or alternatively a characteristic curve can be analysed into a frequency polygon.

(3) In both the above cases the dose per individual is known but in the case of small organisms it is only possible to expose groups to a series of concentrations of a drug and to estimate the percentage incidence of response. In this case it is obvious that the variation in response may be due either to variation in drug uptake or to variation in regard to the effects produced in different individuals by different quantities of drug fixed. This method appears at first sight to be much less accurate than the former methods, but in reality there is not much difference, because when a drug is given to a mammal its action ultimately depends upon the amount taken up from the blood by the tissue upon which the drug exerts its action. Hence in all cases the individual variation observed may be caused by one or both of two factors, variation in uptake of drug by cells and variation in the cellular response when the uptake is equal.

(4) Individual variation also can be studied upon isolated organs and in this case two types of measurement are possible.

(a) Determination of the drug concentration needed to produce a selected effect on each of a series of preparations.

(b) Measurement in a series of groups of the amount of some graded action produced by a series of concentrations.

It may be stated at once that similar problems arise whichever method of estimation is chosen. With all the methods mentioned some drugs produce symmetrical sigmoid curves and other drugs produce markedly skew distributions of variation.

Fig. 53 shows a symmetrical distribution of variation over a moderate range. Such curves are easy to describe, because the median is equal to the mean in the case of symmetrical distribution of variation, furthermore the standard

\(^{1}\) Wijngaard en, L. Van: Arch. f. exper. Path. 113, 40 (1924).