WHAT IS NORMAL?*

Physiology is the study of the normal functioning of the body. But what is meant by the term 'normal'? *The Concise Oxford Dictionary* defines the word as, '. . . conforming to standard, regular, usual, typical', and later as, '. . . the average or mean of observed quantities'. It is a term used and accepted every day but in biological science it has perhaps a more exact meaning.

In society a man acts, or is called, 'normal' if he is conforming to the standards of society. These are varying standards — varying with time and with place. The standards by which the normality of behaviour, ethics, morals, sex activity, dancing, art, or any human activity is judged are purely arbitrary and set up by convention and often by prejudice or bigotry.

In physiology and medicine 'normal' has a more precise and less transient meaning. A normal value, or a normal appearance, is something based on either measurement or deduction or both. This paper treats of 3 aspects of the normal, viz.:

1. How does one decide what constitutes a normal value?

2. How does one establish the precision of a normal value?

3. How does one decide whether a measured value is normal or abnormal in relation to the normal?

* This article is based on one of the introductory lectures in physiology for science and medical students at the University of Cape Town.

I

Before an answer is given to the first question it may be of profit to discuss some aspects of the 'scientific method'. Here is a simple and very ancient example of logic:

All men are mortal,
Socrates is a man,
Therefore, Socrates is mortal.

This begins with a generalization, continues with a particular instance, and ends with a conclusion inevitable from the previous two statements. It is an example of deductive logic. Another example might be as follows:

Adrenaline raises the blood pressure,
This man has been given adrenaline,
Therefore, this man has a high blood pressure.

This type of deduction is used every day and in all walks of life. Logical consistency is one of the basic criteria of science but deductive logic alone is worthless in natural science. To break this type of logic down all that has to be done is to ask how the initial generalization is tested, whether it is true, and how one knows. If the initial premise is not true, or is open to some doubt, or is not always true, or has only been established by unreliable methods, then no conclusion arising from it, however inevitable, need be true: it is no more reliable than the initial premise.

Note also that the conclusions reached in deductive logic can be directly observed and established without recourse to logic at all.

The process of arriving at generalizations by direct observation of a limited number of particular instances was known in the past as inductive logic. It does not, however, need any logic to see that a conclusion covering every instance cannot of necessity be arrived at from knowledge of some isolated instances. The inference is possible or, at best, probable, in contrast to the certainty of deductive logic.

Actually, the process of induction, that is the recognition of a generalization or principle from examination of particular instances, is not a process of logic at all but of inspiration, intuition, or invention. It is an unconscious process which results in the formation of a hypothesis. Logic is then called in to test the hypothesis. This type of logic is used to greatest effect in natural science and is termed 'hypothetical-deductive logic'. For example, take the original syllogisms and alter them slightly, as follows:

If all men are mortal,
And Socrates is a man,
Then Socrates is probably mortal.

Or

If adrenaline raises the blood pressure,
And this man has been given adrenaline,
Then this man probably has a high blood pressure.

These syllogisms now begin with a hypothesis, continue with a particular instance and end with a qualified conclusion which may or may not, in fact, be true. If the conclusion, which is verifiable, is false, then the original hypothesis is rejected. If, however, the conclusion is true then the original hypothesis may be true. It may still be false, giving a true conclusion for the wrong reason. For example:

Hypothesis: Smoking causes lung cancer,
Particular instance: The number of people who smoke is increasing,
Conclusion: The number of people with lung cancer is increasing.

The conclusion reached is ascertainably true but the original hypothesis is extremely problematical to say the least, the true conclusion arising from other reasons most likely quite unrelated to the original hypothesis at all. This is also an example of spurious correlation, which is another story.

The testing of a scientific hypothesis requires deduction of every possible observable conclusion from it and comparing these with actual observation. If the hypothesis is a fertile and useful one it will lead to a large number of diverse conclusions which fit with observed facts, and the truth of the hypothesis becomes more and more probable, but it is never certainty. If the hypothesis is false, sooner or later it will fail and must be rejected or amended.

The testing of a scientific hypothesis is not always best done by its formulator, who may fail even to recognize an observed fact which is at variance with his brain-child. Perpetuation of inaccurate hypotheses also occurs because people learning a hypothesis as a fact during their formal education may thereafter refuse to alter their thinking through prejudice, ignorance, or sheer laziness. So many examples of this are available in natural science that it would be superfluous to mention one.

The methodology of statistics is a hypothetical-deductive procedure applied to quantitative problems. Discussion of some simple statistics is, of course, the whole point of this discussion. Be clear that by statistics one does not mean the '37 - 21 - 35' of the beauty queen. Those are not statistics, they are measurements or data. From them is derived the statistic that the lady is in pretty good shape! Here is an example of how statistics may be used as a hypothetical-deductive logic process:

A worker is investigating whether men are taller than women. This is done by measuring the heights of a group of men and a group of women. From these measurements is calculated the average height of each group and the variation in the measurements. The investigator finds that the average height of the group of men is greater than the average height of the group of women.

Then is set up what is known in statistics as a 'null hypothesis', which, on the pattern of our earlier syllogisms, might be something like this:

Hypothesis: If men and women are on the average of the same height,
Particular instance: And in this investigation the average height of the men was X inches and that of the women Y inches,
Conclusion: Then the difference between X and Y is probably purely from chance.

Simple statistical methods are then used to ascertain the probability that the conclusion fits with the observable facts. In other words, the odds are determined that the conclusion is true.

If the probability is high then the hypothesis is retained and the worker can say, 'On the average, men and women are the same height' or 'The difference in height found between men and women is not statistically significant'.

If the probability works out low then the hypothesis is rejected and the worker can say, 'Men are taller than women' or 'There is a statistically significant difference in height between men and women.'

The criterion of high or low probability is the only arbitrary measure in the analysis and of this more is said below.

Familiarity with statistical methods is indispensable to any scientist, medical practitioner, or student. Without some understanding of statistics he is like a soldier going into battle without a gun.

There has been a slight departure from consideration of the first question — How does one decide what constitutes a normal value? — but the point of the discussion will soon be apparent.

Consider the red-blood-cell count per c.mm. in healthy males as the normal value to be established. The total possible number of any one type of person or object is known as the *population* of that person or object. Naturally it is not possible to measure the RBC count in every member of the population being here considered, and hence the process of induction must be followed. The measurements are made on a sample of the population and from these is induced a hypothesis for the total population.

It is assumed that the method of measurement gives reliable and accurate figures. If it does not, then any hypothesis or subsequent conclusion is invalid. No conclusion can be any more accurate than the method of measurement.

The sample that is measured should be what is known as a *random sample*, that is to say any member of the population must have as good a chance of being picked for the sample as any other member of the population. In the particular case being used as an example this is, of course, difficult, if not impossible, and of necessity there will be a sample which, depending on available resources, is more or less a *biased sample*. The larger the size of the sample the less chance there is of errors arising in any conclusion from this reason; in other words, the smaller will be the *sampling error*.

The data are thus collected from the sample of, say, 150 healthy males, and the readings are added together and divided by 150, the result being the average or *arithmetic mean*. The result is, say, 5·4 million RBCs per c.mm. The normal has been decided.

II

But how does one establish the precision of this normal value? Does it mean anything? Is it anywhere near the truth? If every measurement which was taken from the sample had been exactly 5·4 million per c.mm. then that figure could have been quoted as the normal value with a fair degree of confidence. However, it is a characteristic of living organisms that there be variation one from another and while the description of a set of data may be begun by calculating the mean, this single statistic obviously fails to reflect the variation that is present among the separate measurements. For example, a paper appeared some years ago describing a condition which the author, in his conclusions, stated 'was most prevalent at about 40 years of age'. It turned out that this figure had been arrived at by his having had two cases, one in a 6-month-old infant and the other in an 82-year-old man. Such sweeping generalizations are still, unfortunately, too common in reports from clinical medicine.

It is fortunate that description of the element of variation does not require that each of the separate items be named. Some people give a mean of their data and then add the range of measurements. For example, 'Height of 20-year-old men: mean 5 ft. 9 in., range 5 ft. - 6 ft. 5 in. On the face of it this seems better than a bare mean, but it still does not provide the information required, which is the precision of the mean.

A simple and exact scheme for describing variation is available since within almost all groups of biological data the measurements show a common pattern of distribution about the mean. Most of the measurements in a given group cluster around the mean, and then, as the distance on either side of the mean increases, fewer and fewer measurements occur. This known as a *normal frequency distribution*. It is illustrated graphically in Fig. 1. From

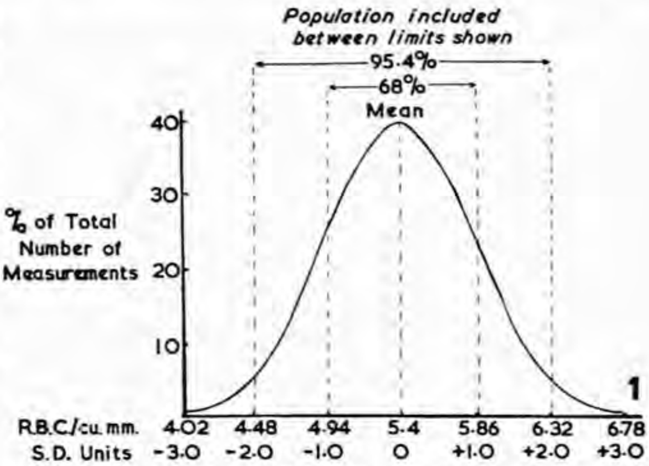

Fig. 1. The standard normal distribution curve.

any set of data it is now simple to calculate a single number which, when added to and subtracted from the mean, will mark out an interval which will include a known fraction of the total number of measurements. This statistic is known as the *standard deviation* or *S.D.*. Calculation of this figure is based on the deviations of individual measurements from the mean and it is given by the following simple formula:

$$\text{S.D.} = \sqrt{\frac{\Sigma(\bar{x}-X)^2}{N-1}}$$

Where $\bar{x}$ is the mean
X is each individual measurement
N is the number of measurements
Σ signifies 'sum of'.

Thus it is possible to write 'The normal RBC count in the healthy male is 5·4 million per c.mm. ± 0·46 S.D.

It should be noted that this is one of the few correct uses for the symbol (±). This symbol should never be used as shorthand for the term 'approximately' — it is incorrect and misleading.

An interval limited by one S.D. unit on either side of the mean, that is between 4·94 and 5·86, includes 68% of all measurements; two S.D. units include 95·4%; three S.D. units include 99·7% (Fig. 1).

The normal value has now been described in more satisfactory terms. There is a mean value and a figure giving the variation about this mean as a measure of the precision of the normal value. More can yet be done. From the sample mean can be obtained an estimate of the actual mean of the whole population — or rather the limits within which the sample mean could be at variance from the population mean may be estimated.

The bigger the sample the closer the mean will be to the population mean. The error connected with the mean when it is used to estimate the population mean is called the *standard error*.

The standard error (S.E.) is simply $\frac{\text{S.D.}}{\sqrt{N}}$. It should not be confused with S.D.

Using tables one may decide to any desired degree of confidence the limits within which the true normal value (the mean value of the population) lies.

III

The third and final question for consideration is this: How does one decide whether a measured value is normal or abnormal in relation to the normal?

It is an important medical problem to establish the normal average and degree of variation for various characteristics in order to provide a sound basis for detecting and differentiating the abnormalities of disease.

For example, a physician finds the RBC count of an adult male to be 4·5 million per c.mm. The question he must answer is, 'Is this count abnormally low and should the patient have treatment?'

Statistics can help to answer the question. The statistical question to be answered is, 'What is the probability of picking the patient out of the normal population by chance?'

This question is easily answered if the normal mean and S.D. is available, i.e. $5{\cdot}4 \pm 0{\cdot}46$.

This patient is $\frac{5{\cdot}4 - 4{\cdot}5}{0{\cdot}46} = 1{\cdot}96$ S.D. units below the mean. Since 95% of the population lie in the limits bounded by 1·96 S.D. units above and below the mean the chances, or rather the *probability* (P), of the patient being picked out by chance is $\frac{100 - 95}{2} = 2{\cdot}5$ in 100, i.e. $P = 0{\cdot}025$.

Should this man be considered normal? This is the question now confronting the doctor. This question can be decided only on purely arbitrary grounds. It is conventional to choose one of two probability levels for this decision. Either 5 in 100 or 1 in 100. If the line is drawn at $P = 0{\cdot}05$ then this patient is beyond normal limits and should be treated. On the other hand, if the line is drawn at $P = 0{\cdot}01$ then the patient is not treated as abnormal. Statistics can only give the probability involved. Where normality ends and pathology starts must be decided on a quite separate and arbitrary basis.

This paper is an attempt to indicate the position of statistics in science and medicine, the logic behind statistical methods and their bearing on physiology.

Statistics, particularly biostatistics, is a wide subject but not a complicated one. One must never be shy of statistics but use them well; try to understand them and always appreciate this: Statistics prove nothing, they only help the human mind to come to a conclusion soundly based on the available data.