BRITISH POSTGRADUATE
MEDICAL FEDERATION

# The Scientific Basis of Medicine Annual Reviews 1972



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# PREFACE

Once again this volume of selected lectures on the scientific basis of medicine offers contributions from many disciplines and varied approaches to our fundamental thinking. Subjects range from the broad approach of Sir Harold Himsworth to clinical research in general and Dr Benjamin to epidemiology to detailed laboratory science. Most of the subjects are of topical interest covering practical aspects of immunology and enzymology, as well as facets of cardiorespiratory physiology and clinical pharmacology. The authors are all experts in their own field and we have been indebted to them for their contributions to this series.

Sometimes a lecture is omitted because of a recently published review. Dr D. A. J. Tyrrell who lectured on 'Respiratory Viruses' has given a reference to Stott and Tyrrell, *World Medicine* **45**, 5, 1971.

We wish to thank the *Lancet* for permission to reprint Sir Harold Himsworth's opening lecture which was published in that journal on 24 October 1970.

J. McMichael

## LIST OF PLATES

## NOTE

The reviews printed in this volume
are based on lectures delivered on the following dates:

| | | | |
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# I

# Clinical Research: its Contribution to Biological Thought

SIR HAROLD HIMSWORTH

To those of my generation one has only to mention the words 'clinical research' to summon up the memory of a man who, in our formative years, epitomized the new outlook and confidence that was arising in the field of clinical medicine. That man was, of course, Thomas Lewis.

It was Lewis's good fortune to come upon the stage when knowledge in his field was in process of transition. Just as astronomy had passed from the age of Tycho Brahe to that of Kepler, so clinical medicine appeared to him to be passing from its observational period to one in which purposive investigations were coming increasingly within its reach. Imbued with this conviction, Lewis made it his purpose to propagate these views and to prepare men for the new chapter that he believed was opening before them.

At this distance, and with the medical successes of the last half-century behind us, it is difficult to recapture fully the climate of opinion in those times. Yet it would be worth our while to try to do so, for the implications of the changes that were then occurring are, as yet, by no means generally appreciated and the views he contraverted are still not without their influence.

Broadly speaking, at that time, a distinction was drawn between what was called the art and what was called the science of medicine. The former was considered to be the sphere of the clinician, the latter of the scientist. Corresponding to this distinction, it was believed that there were two different ways by which knowledge in the clinical field could be advanced. One was by the classical method of a practical art which rested

on the progressive accumulation and ordering of empirical observations of natural phenomena as they occurred. The other was by the application to clinical problems of scientific knowledge gained in other fields of investigation.

To regard these two views as standing in opposition to each other would be essentially to misunderstand the situation. On the contrary, they were regarded as complementary and as the natural expression of a state of affairs that was inherent in the situation with which clinical medicine dealt. Nevertheless, acceptance of this assessment of the position implied also the acceptance of its corollary—namely, that clinical phenomena were in some way different from those in other fields and, as such, largely insusceptible to a direct approach by scientific means. It was this that Lewis set himself to contravert.

Yet it is not difficult to see how such a belief could have arisen nor to appreciate why it is still not entirely without its influence.

As Francis Bacon (1620) pointed out at the beginning of the modern scientific revolution, all sciences arise on the basis of some practical art. In their early stages, all are confined to the accumulation and verification of their particular experience. Beyond this they cannot advance until they have gathered a sufficiency of data to allow them to begin classifying these according to their similarities and to produce what Karl Pearson (1892) called a *catalogue raisonné*. Partly because of the complex setting of its problems but, more particularly, because of the difficulty of devising acceptable techniques to investigate these, clinical medicine remained for long restricted to the first of these stages. This was in marked contrast to the situation in the other branches of natural knowledge. In these there were no ethical restrictions imposing a limit on the techniques that were permissible or on the conditions to which the research worker could subject his material. Here, experience could be provoked at will and the investigator liberated from his dependence on the chance occurrence of phenomena. As a result, progress of knowledge in these surged ahead whilst that in the clinical field inevitably lagged behind. It is not surprising, therefore, that clinicians, uneasily aware of this discrepancy, should have come to feel that their field of experience was unusual and to

regard with scepticism those who pressed for a more positive and scientific approach to its problems.

This point of view was, in the opinion of many, supported rather than contradicted by the evident fact that the physical and biological sciences proper were increasingly producing knowledge that could be applied with conspicuous success to the clinical field. The achievements of Pasteur in the field of infections, of the biochemists in metabolic disorders, of the physiologists in the analysis of body function, of the chemists in therapeutics, were there for all to see, and each year saw yet further evidence produced to this effect. In these circumstances it was almost inevitable that scientists and clinicians alike should come to see the clinical field as one which, although offering opportunities for the application of scientific knowledge, was itself insusceptible to direct cultivation by the scientific method.

It was this particular aspect of current opinion that Lewis challenged. Fortified by his own achievements in cardiology, he rejected the idea that these were no more than the results of applying knowledge gained in other fields of science and, constituted as he was, he could not remain silent (Lewis, 1933, 1934).

As it so happened, I was closely associated with Lewis at this time, and I know that he was under no illusion as to the opposition he would encounter if he ventured to put forward his ideas. In this he was not mistaken. I think, however, that even Lewis was disconcerted when a man he respected as much as the then President of the Royal Society (Hopkins, 1935) felt impelled to take official exception to his views and to express profound disquiet at the prospective diversion of talent and resources to the clinical field that he felt these implied.

It may be thought that I have unduly laboured these past events or that a mistaken sense of filial piety has led me to exaggerate their significance. Yet it is clearly of no small importance to medical progress to know whether we are to regard what Lewis called clinical science as an applied subject, confined by the nature of its material to the interpretation of its data in the light of knowledge gained in other fields of scientific endeavour, or whether, as he thought, we are to regard it as a subject in its own right, on a par with any other in the biological

field, and, as such, an essential source of contributions to the understanding of living processes. This is the problem to which I propose to address myself in this lecture, and, if I do so with the benefit of hindsight, that may be all to the good.

## Definition of New Subjects

Perhaps one of the most difficult problems with which a research organization can be faced is that of deciding whether a new subject has emerged or (which comes to the same thing) whether a further field of natural experience has become accessible to scientific cultivation.

In my time at the Medical Research Council, the Council was repeatedly faced by questions of this kind. Almost always these took the form of asking: 'What is so-and-so? What is social medicine? What is biophysics? What is molecular biology? What is clinical science?' And, of course, implicit in any such question is the further question: 'Is there any such thing?'

To answer questions of this kind is never easy. By the time that the issue is raised one is always confronted by two conflicting views. On the one hand is the view of those who hold to traditional opinion and see in the proposed development no more than a variation of their own particular knowledge. On the other is that of the protagonists of the proposed development who feel, always strongly, that the concepts of traditional subjects are quite inadequate and that only by approaching the allegedly new field on its own merits can this be developed. The problem is to decide which is right, for the consequences of an erroneous decision are never negligible.

It was the late Wilfred Trotter who once defined quackery as the result of the premature attempt to apply the methods of a science to the domain of a practical art (Trotter, 1932); and I think this points to one of the two considerations upon which the answer to these problems turns. We can put this in the form of a question. 'Have the data in the field concerned been sufficiently defined to be susceptible to scientific analysis and, if so, are methods available to allow this to be done?' Obviously unless the answer to both parts of this question is in the affirmative, the case will fall to the ground.

The other and equally important consideration is of a different kind. It is: 'Is the field of natural experience that it is proposed to investigate different from that related to other scientific subjects and as such something that can become a source of knowledge that they cannot supply?' If the answer to this question is 'yes', and a new field of natural experience has indeed become accessible, then for this to remain tied to the concepts derived from experience in other fields, cannot but retard scientific progress. If on the other hand the answer is 'no', and we conclude that the allegedly new field of experience is no more than a part of one already under cultivation, then the proper course is clearly to strengthen its links with endeavour in this field rather than to unbalance effort by providing for its independent development.

It seems, therefore, that if we are to answer the question 'What is clinical science?', it is on lines such as the above that we must do so. We must consider first the question of the susceptibility of clinical data to scientific development and then the question of the uniqueness, or otherwise, of the field of natural experience to which these relate.

## The Scientific Method

In any consideration of scientific method, it is important to distinguish between the method of thought employed and the techniques necessary to obtain the data with which this operates. The following two examples will make this clear.

Probably no two subjects of scientific knowledge are as far removed from each other as astronomy and clinical medicine. At first sight, therefore, we might expect that their methods of thought—as distinct from the techniques of investigation they use—might be essentially different. Yet we need only look at an example from each of these fields to see that this is not so.

The example I have chosen from astronomy is the discovery of the planet Neptune, surely one of the most elegant intellectual achievements even of that distinguished science.

In the year 1845, the attention of John Couch Adams, a fellow of St John's College, Cambridge, was attracted by an

unexplained deviation that had been observed in the orbit of the planet Uranus. He was satisfied that the observation was valid and had to be explained. Pondering the matter, he came to the conclusion that this could only be done if there existed another but unknown planet which, periodically in the course of its orbit, came into a particular relationship with that of Uranus. On the basis of this hypothesis, he prognosed that on a certain day in the autumn of 1846, the postulated unknown planet should be visible at a particular position in the sky.

By one of those apparent coincidences that are so common in the history of scientific research, another astronomer in Paris, Leverrier, had followed the same train of thought. The outcome was that, on the appointed day, the German astronomer, Galle, directed his telescope to the indicated point in space and the planet Neptune was discovered.

There you have a classical example of the scientific method: the making of an observation and the establishment of its validity; the formulation of a hypothesis (or conjecture if you prefer) to explain this; the testing of the hypothesis by reference to the natural situation, and the consequent verification of its correctness.

Now let us take an example from the biomedical field that is within our own memory.

Long observation of the disease, rheumatoid arthritis, had left the abiding impression that, once the condition was established, its remission was unlikely. But in the lore that had accumulated around this intractable illness, there were persistent rumours that, if the sufferer became pregnant or developed hepatitis, spectacular, albeit temporary, remission might occur. In the 1940s, Hench satisfied himself that these reports were valid. He was thus driven to ask what it was that two such dissimilar conditions as pregnancy and hepatitis had in common. Once this question was formulated it was a short step to the realization that in pregnancy there was an over-production of certain steroids, whilst in hepatitis their destruction was diminished. The inference was clear. The common factor was a raised level of the steroids in question within the body-fluids and, if the conjecture that the remission might be due to this was correct, it followed that by giving the appropriate steroids

to patients with rheumatoid arthritis and raising this level, a remission of the disease should be induced.

I need not complete the story of how this hypothesis was put to the test and verified. Nor need I detail the good fortune that the biochemist Kendall had, for another purpose, undertaken the systematic isolation and analysis of the steroids of the adrenal cortex so that samples of these were ready to hand. I think, however, that I have said sufficient to establish the point. Although the techniques used by these two subjects were necessarily so different, there was, intellectually speaking nothing to choose between the method of thought pursued by Adams and Leverrier in the discovery of the planet Neptune and that followed by Hench in his discovery of the role of cortisone. That is the first point I wish to make. Before venturing to generalize from it further, however, consideration needs to be given to fields that depend on the experimental rather than the observational approach.

## Experiment

Undoubtedly the experimental method is the most powerful single tool yet forged by man for the advancement of natural knowledge. By it, not only is the investigator liberated from dependence upon chance happenings but he can isolate the phenomenon he wishes to study from its other variables and carry out his investigations under defined and controllable conditions. Further, he can so devise the situations he studies as specifically to test the ideas he has formed and in this way impose a rapid and exacting discipline upon his thinking in regard to the phenomena in question. It should be no surprise, therefore, that the experimental method has come to occupy such a high place in scientific estimation nor that those sciences that can be designated as experimental have come to have in general regard something of an élite quality. But has the experimental method any significance for the advancement of knowledge other than that, in subjects amenable to this approach, data can be obtained more rapidly and precisely than in subjects that are not so fortunately circumstanced?

Perhaps the best definition of an experiment ever made was

that given by one of the greatest, if not the greatest, of all experimental biologists, Claude Bernard. He wrote: 'An experiment is essentially only a provoked observation' (Bernard, 1865). If this be true—and I think that it undeniably is—then whether data are obtained by observing phenomena that occur naturally or from those elicited artifically is quite irrelevant. In either case the data relate to the mechanisms of natural systems. In whichever way we obtain them, we have still to draw inferences and test these against further natural experience, or the contrived experience we call experimental, before we can wring any knowledge from them.

## Applied Science

From the point of view of the significance of their contributions to the development of scientific knowledge, it would seem, therefore, quite wrong to classify scientific subjects according to whether they obtain the data with which they work by observational or by experimental means. From the same point of view, it is even more mistaken to be misled by the fact that the experimental method is practised largely in laboratories and, in consequence, to classify research according to where it is carried out. In regard to medical research, Lewis himself made this point explicitly when he wrote: 'To divide or attempt to divide medical research into ward and laboratory research is narrow and harmful; it is a profound error to believe that there is any essential difference in method however different may be the techniques' (Lewis, 1934).

The conclusion to be drawn from these considerations is clear. Techniques are simply means to obtain data, and the techniques used in a subject are entirely irrelevant to any consideration of its contributions to the development of knowledge.

Stated thus generally, this conclusion may seem no more than a glimpse of the obvious. If we follow it a little farther, however, we may be surprised at its implications. Let us look, for example, at some subjects in the biomedical field.

Epidemiology is concerned with uncovering the reasons that underlie the incidence of diseases in human communities. Dealing with men in the mass, epidemiology is compelled to use