

EDITORIAL

How productive is medical research?

Productivity

One would gain the impression from television programmes or reports in the popular press that medical research since the Second World War has been highly successful overall. One would think immediately about the development of new antibiotics, renal dialysis, the Salk vaccine, organ transplantation, intensive care units, the application of ultrasonics to obstetrics, automatic instrument monitoring and the development of computerised axial tomography. A research worker in the basic sciences would enthuse about the description of the Krebs cycle, the elaboration of the ionic theory of electrical activity, the elucidation of the double helix of DNA, the discovery of cyclic AMP, the development of quantitative immunoassays etc. Some medical research workers feel some of the pride for these advances. Fortunately, successive governments and the public have shown by their continued financial support of our endeavours, that they believe we all share some responsibility for the progress made.

In the world as a whole, billions of dollars are spent annually on medical research. In Britain alone, according to the latest figures available, the Government spent about £66,000,000 on health and medical research (1975-1976) and industry spent about £43,000,000; they employed 6,500 and 9,000 personnel respectively. In addition, a substantial proportion of hospital, academic, technical and secretarial staff of medical and biological departments of universities and polytechnics are also engaged in research. Of course, these figures represent only a few per cent of the total personnel and funds employed in this activity throughout the world.

Yet when we look at some of the most pressing problems of medical research, for example, the biology of coma, the mechanism of ischaemia, the genesis of cancer, the biochemical loci of schizophrenia, multiple sclerosis and ageing, or even the mechanisms of action of most drugs (as opposed to their sites of action), we are forced to the conclusion that our research overall is either remarkably unsuccessful, or exceedingly inefficient. Much of the most newsworthy results of research has been applied to only a very small proportion of patients afflicted by serious disease.

Fundamental problems

- (i) Disease, especially if it is debilitating, often affects the patients' life styles and physiological functions so profoundly that it is often difficult to find suitable 'control' subjects with which to compare them. This is particularly true in respect of the biology of dying, coma and head injury.
- (ii) Since the overall validity of any experiment or observation depends upon the validity of every major assumption upon which the interpretations of the results are to be made, it behoves us to attempt to identify and validate every one of them. If, as is usual, one's own experiments follow upon the work of one's predecessors, one's employment or citation of their findings also implies willy-nilly (but often unknowingly) that one accepts the validity of every major assumption that they have made.

(iii) In biochemical, pharmacological and anatomical research in particular, far too little attention is paid to how the techniques of examination of tissues from living persons or animals may themselves affect the result of experiments qualitatively and quantitatively.

(iv) When research workers find that results of experiments *in vivo* are in apparent disagreement with findings *in vitro*, they often do not attempt to resolve the apparent discrepancies. For example, ouabain can be used for the treatment of heart failure, yet all pharmacologists believe that it blocks the sodium ion pump. Aspirin uncouples oxidative phosphorylation *in vitro*, but is used daily in large quantities for many diseases. One could give a very large number of other examples.

(v) Pathological material cannot usually be obtained from autopsies before several hours after the patient's death, during which time much autolysis has occurred. When one uses experimental material from animals, one often has no way of knowing the relevance of findings from them to human beings, especially when the animals have been subjected to 'models' of the human disease, rather than to the disease itself. The only ultimate method for assessing the validity of a 'model' is the testing, probably some time in the future, of the relevance of the findings from it to the treatment of disease in patients.

(vi) Pharmacologists recognize the importance of the variation of sensitivity to drugs by different species of animals, but they often study the action of drugs at concentrations very different from the therapeutic range. They may justify this either by pointing out this problem of species variation, or by noting that it is very often difficult to know the concentration of a drug at the target organ or 'receptor'.

(vii) Many studies, like that of Gore and his colleagues in the *British Medical Journal* (5th January 1977), have shown that statistics are widely used inappropriately. The understanding and use of statistics is nowadays a highly complex technology.

Organizational difficulties

(i) Often a clinician, whose main responsibility is properly to his patients, does not have the time to carry out his own experiments, so he employs recently graduated physiologists or biochemists who do not have experience. Furthermore, many well-known and senior research directors are too busy with administration and travel to concern themselves directly with the raw data and their interpretation, or even to read the burgeoning volume of literature. The person who usually carries out the experiments is often a junior assistant or a technician, who does not have the intellectual responsibility for the experiments themselves. Thus, among the list of authors of papers, it is sometimes difficult to identify the person who can and will discuss the fundamentals upon which the value of the experiments depends.

(ii) Clinical research is so difficult that many graduates, who start out by wishing to investigate human disease, gradually drift into the much easier fundamental biochemical, physiological and pathological studies of the tissues affected by the particular disease. They justify this by urging the undoubted truth that we must understand the tissues more thoroughly before we can decide about the nature of the aberrations which represent disease.

(iii) A substantial proportion of Ph.D.s and M.D.s continue to work on the same subjects as those upon which they wrote their theses, because they feel most confident in these areas. Sometimes, when they embark on their postgraduate studies, they do not know enough about the projects to which they have been assigned to be able to assess

their value, and by the time they have sweated through a thesis, they are too intellectually committed to their own work to look at its fundamental validity objectively. Furthermore, when they become supervisors in their turn, they frequently perpetuate study on the same subject.

(iv) Most doctors, who have not taken a degree in a basic science during their undergraduate medical courses, do not have specific training in research methods.

Personal reasons

(i) Seeking after 'truth' is not the only motive for going into medical research or academic life.

(ii) Questioning conventional wisdom may put one's grant applications or career prospects at risk.

(iii) Few research workers have even been prepared to recognize that the problem of overall poor success in research work exists at all.

I would like it to be noted that I have not mentioned lack of resources, as this paper is written mainly in relation to advanced industrial countries, where I believe this is a relatively minor factor. Nevertheless, it seems probable that the problem highlighted here, and the explanations of its origins, are relevant to medical research in many other countries.

Towards a solution

There are many measures which could be taken, which might improve the situation. More clinicians should be encouraged to go back to courses in fundamental sciences, and more fundamental scientists should be encouraged to study again the rudiments of pathology, physiology, biochemistry and biology. This would require in most countries an expansion of the facilities for clinicians to take sabbaticals on full pay and without loss of seniority, to learn research techniques. There should be many more short courses for clinicians who wish to learn research techniques and pitfalls applicable to critical appreciation of the clinical results they are finding themselves. This should improve the quality of clinical research overall.

Audiences at meetings where clinical advances and findings are being discussed should be much more vocal and critical. Often if criticism is driven home before the research worker has invested too much time or effort in a project, it may be modified or stopped. This can only be to the good of the discipline as a whole. It would also improve the atmosphere for critical but not unhelpful intercourse if a much larger ratio of scientific meetings was informal and not published.

Many more scientific journals should encourage dialogue between authors and referees. Writing private letters to authors of books or papers is often of considerable mutual advantage. The practice of coupling criticism of a paper with the author's right to reply is useful and spreading.

Finally, I think, we need a few more Devil's advocates in the system. Idealism is an old-fashioned virtue which needs to be cultivated much more in research circles.

HAROLD HILLMAN