Medical Research

A view from the coal face

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We should all be grateful to Dr Richard Smith for his exhaustive review of the medical research scene in the United Kingdom. Hitherto, what information we have has had to be culled from many publications: some of this information has been accessible and hence widely quoted until it has evolved into accepted wisdom. This information is not always the most accurate, and perspectives have therefore tended to become distorted. Most of us are seeing much of the remaining data for the first time. It is valuable to have all this put together, yet disconcerting to see the obvious gaps in the picture and to leave feeling with Dr Smith that the only consistent pattern is one of demoralisation and fear for an uncertain future. Because the statistics are misleading and because assessing research is frequently a matter of value judgment rather than numerical analysis, I would like to present a personal view of the clinical research scene. I purposely choose the coal face in preference to the more fashionable grass roots analogy. No shafts of sunlight help the genuine face worker: if he sees a distant light it will come from a torch borne by others whose credentials are probably as doubtful as his. They may or may not be leading the way to more productive seams.

Demoralisation and uncertainty

Scientific research is recognised by the present Secretary of State responsible for it to have an "outstanding record" and to be a "major national asset."¹ Almost at the same time the House of Lords Committee on Science and Technology has reported that medical research suffers from "low morale, even despondency."² Most of those who work in academic circles would vouch for the truth of both these statements—that is, the record is impressive but the present state deplorable. What, then, is the cause of the present discontents? The Lords' committee identified one overwhelming cause, the low value attached by the present government and its immediate agencies to the sort of scientific research that we have been accustomed to carry out. This said, objective measures of decline prove curiously elusive. On some measures of productivity or funding we do not come out too badly in comparison with our competitors (although investment by industry in research is universally accepted to be abysmal). Where worrying evidence of inadequate funds is shown—for example, in the failure of the Medical Research Council to fund alpha rated projects—these problems seem even greater in the United States.

I will say more of the influence of the present political philosophy below. But to attribute all our problems to it is to be guilty of superficiality and also of a rather naïve optimism—the belief that,

given a change of heart (or of leadership) all will be well again. It will not. To understand this we have to look at what the medical research community is trying to do. There is a strong impression that they do not know themselves and that the most confused group of all comprises the clinical researchers. To understand this we need to examine the changing relation between science and clinical practice as each develops at an unprecedented rate.

The attack on science and learning

The debate about the relevance of basic science to medicine has now assumed a public face. Clinical scientists have found themselves willy nilly defending the generality of science against a government inspired questioning of its value. Richard Smith finds the evidence contradictory. This is not surprising as the position is by no means as simple as some advocates would have us believe. Two arguments in defence of science are used: they are both persuasive, but quite distinct.

The first defence of science is based on its role as an intrinsic part of our culture. This is the argument justifying the universities put forward by Newman among others when he declares that "knowledge is capable of being its own end."³ Until recently there has been as near a consensus on this defence of learning as there has been on any aspect of education. But this argument is not, of course, confined to science: it attributes value to the arts, literature, and philosophy. Education in this sense was felt to strengthen a person's powers of thought, expression, and imagination and to interpret his or her experience in the light of culture and history. All this is now threatened by default rather than by a frontal attack.

The state of clinical and scientific departments in our universities is nothing compared with the demoralisation of the arts as universities seek to sustain those departments which seem to bring in short term financial gains. In many of our universities philosophy departments are now extinct: arts departments have been progressively weakened and amalgamated. We are in other words seeing the abandonment of an accepted truth about the nature of learning which predates the Renaissance. Ironically this revolution has been accompanied by desperate and radical attempts to reform school education in the face of evidence for declining standards of literacy and numeracy. I mention the need to defend learning in its broadest sense against the present governmental attack because such arguments seldom figure, to our communal shame, in the defence of science: we seem to have yielded half the argument.

Basic and applied science in medical research

The second argument in the defence of research is a more familiar one in the present climate. According to this, research in basic science ("curiosity led") has frequently produced important economic applications, which were not predictable at the time the research was started. As Dr Smith points out, studies that have tried to show this have reached confused and contradictory findings,

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one suspects powerfully influenced by the preconceptions of the researchers. We should all be particularly grateful to Dr Smith for his analysis of the flaws in Comroe's and Dripps's work,⁴ which is so often cited if not actually read. Unlike Dr Smith, however, I am not convinced that there is a need for more and better of the same thing.

A numerical approach to the history of science is not particularly helpful. Nothing is more pathetic than the laboratory scientist applying the methods of experimental science where they do not rightly belong. It is faintly reminiscent of Newton's mercifully forgotten writings on theology.⁵ Some of the flaws in these studies are documented by Dr Smith. The important fallacy, however, is implicit in the design of the work. It would seem axiomatic that work that immediately precedes a seminal development is more applied in nature than work remote in time from it. The development of diuretics as antihypertensive agents, for instance, was not the motive for William Harvey's studies of the circulation of the blood nor did it motivate the numerous individuals who later developed means of measuring blood pressure. Clinical trials of diuretics in the 1950s were, however, more applied in nature. Where does one draw the arbitrary line in tracing the intellectual ancestry of an idea? I suspect that what Comroe and Dripps were testing was the historical consciousness of their experts or, alternatively, the tautologous proposition that the further you move back in time from an event the further you are from it. The important danger with studies of this sort is that, by testing the obvious, they give the impression that there is doubt about it. There should not be. A moment's thought would show that any new drug or diagnostic technique owes its development to a body of scientific research that beomes less "goal directed" the further back one goes.

Unfortunately, the importance of "non-goal directed" research is not challenged now, even by Mr Baker.¹ What is under challenge is the economic value of such research to this country. According to this view, a large investment by the research councils and the universities in the 1960s and 1970s in scientific research produced little in the way of value as shown by the economic decline in this country over that time. The postulated reason is that economic success is dependent not on the ability to make important scientific discoveries but on the capacity to exploit technical change. Cairncross summarises this influential philosophy.⁶ Exploitation of new technology is, he says, "a commercial operation that may owe little or nothing to science or to research and development but a great deal to borrowing or adapting what is already known." And how, one wonders, are those who exploit technology to be educated? Will this be in the universities or the market place?

Problem of the growing volume of potential research

Yet there is, behind the current heart searchings, a real problem for medical researchers that has proved sufficiently uncongenial to be ignored. The range of possibilities for valid scientific investigation is now so great that we can no longer entertain the principle of supporting "good science" in the hope that unpredicted beneficial discoveries may be made. As a crude estimate of medical research activity consider the average number of pages of *Index Medicus* issued each month. Between 1930 and 1960 (allowing for changes in format) the number of pages was fairly consistent at 200 a month. By 1970 the number had increased to 757 a month, by 1980 to 1024 a month, while in January 1987 there were 1505 pages. Each page lists 80-90 papers: even allowing for duplication the sheer vastness of modern scientific productivity is frightening. In addition to the increase in volume the inflation of cost is probably several times that used by the government when it applies the cost of living deflator to its allocations.

The hard logic of all this is that there must be constraints and selectivity. It is futile for scientists to echo Hillary when challenged and say that a problem has to be tackled because it is there. There is now far too much there. The questioning of scientific activity on these grounds will inevitably outlive doubts emanating from a fashionable but essentially ephemeral economic theory. We can no longer avoid defining more closely the direction in which we are going.

"Rationalising" the support of research

But how can this be done? Most, but mercifully by no means all, of the strings are held directly or indirectly by the state. To the outsider the present system seems chaotic with a complex web of government agencies and quangos operating in an overlapping way. Richard Smith sees the best hope to lie in getting together the research funds of the health departments, the regions, and the University Grants Committee and giving them to the Medical Research Council on condition that it develops a more rigorous method for setting priorities. Neat administrative structures may seem logical on paper but are disastrous for those who try to operate them, as anyone who has worked in the National Health Service over the past 15 years will appreciate. This is even more true of academic activities, where individual values and goals are even less rigorously defined.

I have now sat on several national bodies that fund medical research. Each has had its own well developed orthodoxy, which depends on its membership and is unrecognised and self sustaining. A self sustaining orthodoxy is, of course, generally true of committees, which tend to unite against outside criticism and reproduce themselves by a carefully regulated succession. This innate conservatism is reinforced by selecting referees from a pool of people of similar outlook. Such groups soon convince themselves that they are working for the best of all possible worlds, even if that world is clearly different in each case. There is no intrinsic danger in such a conviction, as long as several such bodies exist and as long as we do not convince the others that we are indeed the vessels of revealed truth.

There are also less tangible if more sinister forces at work in grant giving bodies. As clinical research declines the number of workers in any particular discipline is small, and they tend to form a well knit group. The danger is that such groups come to regard a discipline as their property; this is all the more likely when funds are tight. It is an illuminating experience to hear the same project grant application discussed unwittingly by two grant giving bodies. The situation is not dissimilar from editing a journal. The extremely good and the extremely bad papers tend to be recognised as such. The rest, which lie in the intermediate zone, elicit different and often extremely discordant judgments. When Dr Smith can reduce editing of journals to a precise science I will accept his suggestions for making the giving of grants more objective. Until that day the multiplicity of funding bodies in medical research is a safeguard for us all, although it is largely an unrecognised blessing that the tidiers would like to regularise. This is one reason (among several) why I support the House of Lords' proposal for a National Health Service Research Authority.

The low esteem for research

Although I part company with Richard Smith on such matters as these, I share his depressing view of the low esteem, indeed hostility, with which research is held by some administrators and clinicians. This is no new event. The British tradition since the mid-nineteenth century among the medical profession has been to resolve the conflict between clinical practice and research in favour of clinical practice. This was bemoaned by Huxley when he told his medical students that "Professors must live: to live they must occupy themselves with practice, and if they occupy themselves with practice, the pursuit of the abstract branches of science must go to the wall."⁷ This was the philosophy alluded to by Flexner when he stated that science was for the British physician not "the breath of his nostrils."⁸ More recently, it lay behind Platt's scathing comments on the activities of clinical university departments.⁹

The reason for such tensions lies in the heterogeneity of medical research. At one extreme is the most applied form of clinical science, which has given us such important benefits as artificial hip replacement, coronary artery bypass grafting, and intensive care. Credit for all these important advances is due to innovative practising clinicians supported by scientists and technicians. These developments are as important in their own way and just as much

part of legitimate "scientific" activity as any discovery in basic, laboratory science. This needs emphasising because a new orthodoxy has tended to develop in some circles which demotes such applied science in a hierarchy of values that places advances in basic science at the apex. This is a singularly shortsighted outlook. The technology of science and clinical practice has grown to such an extent that advances can be made only on the basis of mutual respect and partnership. My own intuitive feeling is that this respect is a commodity that has become considerably scarcer as funds have become more tight, with growing concern from clinicians that some basic scientists are using a spurious medical relevance as a passport to survival. The fault lies with both basic scientists and clinicians. An equally great responsibility lies in the neglect of research by the National Health Service, as the House of Lords Committee on Science and Technology rather forcefully pointed out.² This is the second reason for supporting the suggestion of a National Health Service Research Authority.

The change in the nature of research

I have pointed out that the volume of research has increased enormously. The nature of research in medicine has also changed. It is easy to pay lip service to this fact and then ignore the consequences for the rather archaic institutions of medicine. Laboratory methods, clinical trials, and epidemiological studies are vastly more sophisticated and time consuming than they were 20 years ago. One person's skill is rarely enough to carry through an important piece of research single handed. We have left behind the phase of the gifted amateur, just as the age of Darwinism saw out the clergyman-naturalist of the nineteenth century. We are unfortunately left with structures and institutions created in earlier days. A professor or senior lecturer, aided perhaps by a lecturer or one technician, is expected to carry the torch in his own particular specialty. At the same time he or she provides a clinical service, teaches undergraduate and postgraduate students, and acts as a pillar of the tortured health service committee structure.

The conventional answer is provided by another cliché, the "need for critical mass." I share this piece of modern dogma if what is meant is the development of a stable, dedicated group of clinicians and scientists working on a common clinical problem. My concern about the concept of critical mass is the ominous tendency to take it to extremes. Centralisation of research in a few institutions carries the near certainty of strengthening current orthodoxy. It may be argued that we have successful large institutes already (such as the National Institute for Medical Research at Mill Hill and the Imperial Cancer Research Fund Laboratories). The difference between the position of these institutes and the present proposals is that the institutes have hitherto coexisted with strong university departments in related disciplines elsewhere in the United Kingdom, which provide not only people but ideas and criticism. They have not developed at the expense of university departments.

It is also worth bearing in mind that collaboration between scientists and clinicians does not require that they work under the same roof. International collaborations are now commonplace in medical research. Relevant ideas and methods have a habit of appearing in the most unlikely places: the pay off comes from recognising the potential of new developments not in having the right sort of neighbour, who may in any case be too busy with his or her own research programme. The research institute is no more a consequence of the "critical mass" hypothesis than is the development of a megahospital a logical outcome of the recognised inefficiency of the cottage hospital. Something in between is required. Those who have any concern for the health of medical research should oppose centralisation tooth and nail.

What then is to be done?

Academic clinicians are better at diagnosis than treatment. My conclusions are rather different from Dr Smith's, although I agree with him on some important points. I believe that those of us who

are concerned about the future of clinical research in this country should address three influential groups: the government, the funding bodies, and ourselves.

GOVERNMENT

I see no prospect for improvement as long as university departments are depleted of staff and funds. A life supported by a succession of short term grants for your work, or even yourself, with the likelihood that a single failure will prove fatal is no alternative to a secure career in the NHS regulated by the Joint Planning Advisory Committee. The Association of Clinical Professors of Medicine calculated that a sum of just over £17m would reverse some of the worst effects of the University Grants Committee cut backs by replacing some, although not all, of the lost staff.

It is a fair presumption that the government would resist any increase in funds for the support of science. There are, however, aspects of medical research that carry a specific advantage in the argument. Firstly, even the present government has shown itself susceptible to pressure when exerted by enough influential voters. The great success of some medical charities suggests a good deal of popular support for medical research. It is surely possible to hammer home the message that charitable giving to research can work only if there are adequate numbers of creative, well motivated researchers to whom the money can be given: to use the popular jargon, an infrastructure is necessary.

The second point is more politically sensitive, but there are reasons to believe that sympathy exists for it even in the present administration. The comparability of state investment in scientific research with that of other countries is, as Dr Smith points out, disputable, although industrial investment is deplorable. On most criteria government investment is not rising as fast as in other countries and, if salary increases and items of specific expenditure (such as AIDS and a new Antarctic survey vessel) are excluded, it is falling.¹⁰ By contrast, our expenditure on defence stands at the top of the league of countries in the Organisation for Economic Cooperation and Development, as the present minister responsible for higher education pointed out before he joined the government.¹¹ There is no shortage of contemporary examples of countries that have given the highest priority to armaments while investment in institutions of learning has declined. Few of these are congenial and there is no reason to believe that they would commend themselves to the more educated sections of the Great British public, who might recall Jonathan Swift's words on finding a magazine construction in Phoenix Park:

Behold! A proof of Irish sense.
Here Irish wit is seen:
When nothing's left that's worth defence,
We build a Magazine.

FUNDING BODIES

The second group we should consider are those who struggle to be the best of men in the worst of times—those who distribute the funds. We have to recognise that potential medical research far outstrips the capacity to fund it. The unpredictable nature of beneficial outcome cannot be used as an argument to evade this issue and to pretend that all valid research should be pursued. There is, in other words, no escape from value judgments of considerable subjectivity. This places considerable responsibilities on those who assess applications for funds and, I hope, underlines the dangers in any attempt to lump funding bodies together. Fortunately, the independence of the charities (the "jokers" in Dr Smith's pack) will effectively prevent this outcome and enable them to act as guardians against the dominance of received truth. It is to be hoped that the larger charities will develop further their policies of offering longer term career prospects in medical research.

The peer review system is at the centre of research support: the essentially subjective nature of its judgments in my view has to be accepted. Numerical systems of various sorts, including perform-

ance indicators, may assist value judgments (although in rather a limited way) but they certainly will not replace them. It is much more important for justice to be seen to be done.

Allegations of bias and unfairness are, not surprisingly, prevalent among unsuccessful seekers of support. In some cases I fear such complaints are justified: peer reviewers and committees are by no means detached observers. I believe strongly that the transmission of reports both to the applicants and to the other reviewers would afford some protection. The recognition that your written words of judgment are certain to be pored over, not merely by the applicant but also by your peers, is a powerful inducement to care and caution. It is also surely wrong to withhold a careful and constructive critique of his proposals from the potential researcher. The precedent has already been set by most scientific journals: it will clearly be resisted by some grant giving bodies that are concerned about protracted argument and appeal. Such concern is quite unjustified. Editors of journals are not inundated by appeals and, in my experience, no extra staff are needed to deal with them. The other objection cited by Dr Smith to the disclosure of referees' reports is so extraordinary in its implications that it should stand alone: "Furthermore, if we were to change our decision on a project grant in response to an appeal it could only mean in the current circumstances that we couldn't fund something else."¹²

ACADEMIC COMMUNITY

The third group that is influential in determining the future of medical research is the academic community. We have not always proved to be the best of friends. We have tended to join one or other of the besieged camps—the basic scientists, the clinical researchers, the teachers, or the guardians of clinical excellence—and disparage the contribution of the others. Apart from the clear expression of disunity, this gives rise to a widespread view among some of our academic and clinical colleagues that we have no clear objectives at all. In several places Dr Smith's articles would yield support for such a view. There is also now a real risk that we will express our

grief so powerfully that no sane individual could be expected to enter clinical research. It is difficult to attend any meeting on the future of "academic medicine" (the term itself has now acquired pejorative undertones) without the end of the world as we know it appearing as a non-agenda item. It also has to be admitted that some professors and some departments have attached a low priority to research: if teaching and clinical work are to be the sole activities of academic departments there are certainly more secure and probably more lucrative ways of pursuing them. Perhaps those of us in academic medicine who have spent so much time on discussing careers in the health service should contribute some of our efforts to devising a more suitable career in clinical research for changed times. For a start we have to recognise the changed nature of research and of medicine.

In spite of the obvious difficulties, I remain optimistic that this can be achieved. The application of science (in its broadest sense) to clinical medicine is intrinsically so attractive that unless we ourselves raise insuperable obstacles through negligence, clinical research will ultimately prosper.

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MATERIA NON MEDICA

Always on a Sunday

As was customary in the 1930s my mother, when expecting her first child, decided on a home delivery and made her preparations accordingly. When she consulted her obstetrician he jokingly suggested that the most convenient time for him to attend would be before breakfast on a Sunday morning: he would be sure to be at home for the call and his game of golf later in the day would not be interrupted. The following are the times and dates of birth of the first and subsequent five children born to my mother in the same room under the same consultant.

8 19 am Sunday 24 July 1932
4 05 am Sunday 14 January 1934
6 20 am Sunday 21 July 1935
6 30 am Sunday 9 May 1937
1 15 am Sunday 16 July 1944
NR am Sunday 28 October 1945

A contemporary written record was kept, which is extant for each except the sixth child who was born at approximately 6 am. If it had not been for double summer time the fifth child, and first son, would have broken the record by arriving on a Saturday. As it was, he and his brother were in a hurry and each arrived before the consultant reached the house.

Statistically, there being seven days in the week, there is a one in seven chance of being born on a Sunday. Although true for each individual, when extrapolated to a family of six this becomes one chance in 117 649 that each will make their arrival on the same day of the week. When narrowed still further by extending the parameter to arrival between the hours of 12 midnight and 12 noon this becomes a chance happening of 1 in more than 7 million (7 529 536). What can my mother have done to accommodate her consultant so effectively? Apart from taking castor oil before the birth of her

first child and climbing the Wrekin, Shropshire, when her fourth daughter was two weeks overdue, my mother assures me no inducement was used to control the births in such a way that each of her six children should be delivered before breakfast on a Sunday morning.—R BARKER, Dundee.

Timber is sometimes primed with acrylic and oil based paint, including one containing pentachlorophenol. Has this product ever been linked with IgA nephropathy in workers using it?

I do not know of any association between IgA nephropathy and exposure to chemicals at work. In any individual case it would be important to establish whether the earliest manifestations of the disease predated or occurred after exposure to the chemicals in question. Priming timber necessitates exposure to solvents that may produce lassitude or, in extreme cases, narcosis. Careful inquiry about the working conditions and about the relation of symptoms to work should help to establish any connection between a person's symptoms and his exposure to the suspect chemicals. Pentachlorophenol irritates the skin, eyes, and upper respiratory tract. It also decouples oxidation and phosphorylation, leading to an increase in metabolic rate with hyperpyrexia, sweating, and dyspnoea. Again, the relation of symptoms to exposure should be explored and inquiry made into the working conditions. People handling pentachlorophenol have been reported as having reduced glomerular filtration and tubular function (measured by phosphate reabsorption) during periods of exposure.¹ It was not suggested that this was linked to IgA nephropathy.—W R LEE, professor of occupational health, Manchester.

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