THE ROCK CARLING FELLOWSHIP

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The Rock Carling Fellowship
was founded as an annual memorial
to the late Sir Ernest Rock Carling,
for many years a Governing Trustee
of the Nuffield Provincial Hospitals Trust
and Chairman of the Trust's Medical
Advisory Committee

Each holder of the fellowship
will seek to review in a monograph
the state of knowledge and activity
in one of the fields in which Sir Ernest
had been particularly interested and which
is within the purposes of the Trust.
The arrangements provide that the
monograph will be introduced by a
public lecture to be given at
a recognized medical teaching centre
in the United Kingdom

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I

The application of science to medicine

Science and medicine have always been closely linked but never completely united. As chemistry grew, in part, out of the experiments of the alchemists, so medicine evolved from a mixture of witchcraft and observation of sick people. The paths of science and medicine often crossed. It was not rare to find a physician making a contribution to the natural sciences or a physicist or chemist making a successful foray into biology. The enormous development of chemistry and physics in the nineteenth century led to increasing specialization in science and many of the discoveries made in that era were not matched in biology and medicine until the twentieth. Yet when the scientific revolution hit medicine, its impact was overwhelming. Diagnostic methods, therapeutic procedures, and drugs changed beyond recognition, then changed again and again, sometimes within a decade. The medicine of 1978 would be almost unrecognizable to the physician of 1938.

Some of the early achievements in the treatment of infections were so miraculous as almost to surpass belief. They, literally, changed the world. The watch and wait while the pneumonia of a young adult progressed through crisis to lysis or death. The agony of a child with acute otitis media, or worse still, osteomyelitis. The long-drawn-out vigil of the patient with pulmonary tuberculosis coughing away his life. Antibacterial chemotherapy made the cure of such scourges almost a matter of routine. It was a time of optimism. Science appeared to have the salvation of the world in its hand and mankind could look forward to an era of healthy ease and modest luxury. The budgets of the Medical Research Council and the National Institutes of Health increased exponentially and journalistic comment about medical research was almost always eulogistic. I had a very minor part in one of a series of BBC television programmes entitled 'Your Life in their Hands' during

that period. The message was extremely optimistic. The doctors with their modern drugs and machines would be able to solve all health problems if not today, tomorrow or the day after. Leading politicians of the day put their faith in the 'white heat of technology'.

The mood has changed. Medical research budgets ceased to grow in most countries even before the increasing price of energy caused doubts about the future of affluence. Problems seem larger and solutions to them more elusive. Crash programmes on cancer and stroke have made only a modest impact on their targets. The validity of claims made about past successes are being questioned. Both the morality and the cost-effectiveness of scientific medicine have been challenged. Care in the community seems more readily attainable and comfortable than the chance of high technology cure in a modern hospital. The age of optimism has ended.

Amongst the barrage of criticism of medical science, some authors stand out because their arguments have become a focus and a point of departure for others. Two of them have been previous Rock Carling Fellows. When I was asked to write a monograph on the role of science in medicine, in part as an answer to the critics, I felt it necessary to point out that not all clinical scientists would regard me as a loyal defender of the fort. I never signed a letter to *The Times* attacking Rothschild. I am chairman of a grants committee at the DHSS. My research, although founded in laboratory science spreads into human populations. Some of my colleagues regard me as too tainted by the ideas of social medicine and epidemiology to be taken quite seriously. I have even written papers, and conducted research, on the quality of medical care. Gordon McLachlan reassured me a little by saying that the Nuffield Provincial Hospitals Trust had not asked me to lead a counter-attack on every critic of scientific medicine but to propound a reasoned defence and a future strategy. It is a heavy responsibility.

After much thought and helpful criticism from my wife Diana, I have decided to deal with the critics first. If they are right, there is no point in trying to conjure up the Genie of scientific medicine carrying a placard emblazoned 'Dream, mirage, or Nemesis'. If they are wrong, it may be worth while to re-examine the role of

scientific medicine to see how discoveries applicable to medical care are made and used. This is of particular importance in view of the pressure for more applied research. But having done so, I must turn my coat and confess that I find major imperfections in the present mechanisms for the development and application of scientific discoveries to medical care. Whether this is treachery or realism, I must leave the reader to judge.

The most extreme critic of modern medicine, particularly in its scientific aspect, has been Ivan Illich (1), who has claimed that medicine is not only ineffective but directly counter-productive. A few years earlier Pappworth (2) attacked experimental medicine with allegations of cruelty and compared its practitioners to the Nazi concentration camp doctors. Perhaps the most powerful critic of all has been Thomas McKeown (3). His language does not have the extravagance of Illich but his blows are aimed at softer targets. McKeown claims that the achievements of medicine are a mirage and that the fall in mortality which has proceeded for 150 years owes very little indeed to the activities of the doctors in their curative role. Cochrane (4) is another lucid critic of medical practitioners but his criticism is not for being too scientific but for their credulous and uncritical acceptance of each new marvel without bothering to find out if it is effective and efficient. Cochrane's thesis is that all would be well if clinicians and clinical scientists would apply the scientific method to the study of groups and populations by using the technique of the randomized controlled clinical trial. An American research worker once remarked that Archie Cochrane wanted to turn the National Health Service into one giant randomized controlled clinical trial. In the eyes of the general public there is another criticism that finds its chief expression in the columns of newspapers. It is the dehumanizing effect of technology. Where there was a doctor there is now a computer terminal putting questions. At night, instead of a human voice, it's a telephone answering machine. When death comes, will it be needlessly prolonged because someone lacks the courage to pull the power plug of a respirator out of the wall? Yet another view prevails in government. Governments deal with the present and immediate future, not the past. Past triumphs over infection are all very well but that means more elderly people to look after

today. The scientists are pursuing their Nobel prizes in new aspects of molecular biology while the ministers' elderly patients lie in soiled sheets in a Victorian geriatric ward. Should the scientists not be recalled from the frontiers of knowledge and put to work on more homely subjects like the alleviation of backache or the prevention of incontinence?

Targeted research is such an important issue that I shall give a detailed account of how some important therapeutic discoveries have been made. Most contained a major element of the unexpected, and involved integration of knowledge from different areas of science. I anticipate that this will continue to be the case for the medium-term future. Ultimately the advance of molecular biology may limit the importance of surprises, and thereby define the limits of the possible. Until it does therapeutic discoveries cannot be planned in the same sense that a military weapon system or a road network can be.

The complexity and interdependence of the different fields of science applied to medicine have some important lessons for the type of organization likely to optimize the chance of making new discoveries. The minimum effective size of an institution conducting research in medical science is likely to be substantial and cross-disciplinary contacts are of great importance. While I reach an optimistic conclusion about the future contribution of science to medicine, it is as well that both scientists and non-scientists should realize the fundamental limitations. Dead cells cannot be brought to life nor man be made immortal.

Man is an immensely complex organism. Diagnosing and treating human diseases involves complex investigations and treatments. The replacement of clinical judgement by complex machines, at least in some situations, has made medical care seem less human and personal. It has also added enormously to the cost. Doctors have not adapted easily to the changed situation. There is a powerful conflict between their desire to do everything that might conceivably be of benefit to an individual and the need to ration diagnostic and therapeutic resources to a level which the community will pay for.

The least satisfactory part of the application of science to medicine has been in the evaluation of diagnostic and therapeutic

procedures as they are generally used in the process of medical care. The medical profession has been too ready to believe that each new discovery is a breakthrough which can be adopted universally on the basis of limited studies in highly selected patients. There are too few well-designed studies of the real benefits and costs of new and old methods of care. Without such studies better allocation of resources is impossible, and the alternative is a crude form of rationing based largely upon existing patterns. Because of its importance and underdevelopment I shall devote a good deal of space to the subject of applied research and development in the field of health care.

2

The cases to answer

I propose to deal with the arguments of the critics of medical science one by one. If these are formulated as a charge list with the star prosecution witness in each case, it might read as follows:

Charge	*Witness*
Conspiracy against the public	Ivan Illich
Callous lack of concern	Maurice Pappworth
Irrelevance of medical practice to health	Thomas McKeown
Credulous acceptance of new procedures and drugs	Archie Cochrane
Technological inhumanity	The public and the press
Lack of application to real health problems	The DHSS and the politicians

Each one will be heard in turn.

CONSPIRACY

Ivan Illich's book *Limits to Medicine* (1) opens with a challenging sentence: 'The medical establishment has become a major threat to health.' Illich's use of language is extravagant and sometimes quite brilliant. He makes four main charges against the medical care system. The first is concerned with doctor-induced disease. As with much else in the book, he trivializes an important issue by overstatement and inaccuracy. On the one hand he rightly attacks doctors for excessive and careless prescribing of powerful and dangerous drugs. On the other he argues for a less medically dominated world in which patients can make their own decisions about their treatment. In the same chapter he attacks the lack of availability of doctors in rural areas of Mexico and complains that since powerful medicines are available over the counter without prescriptions, the patients take the drugs haphazardly without a

doctor's advice. An advocate who wishes to be taken seriously has some duty to maintain a degree of consistency in argument.

Illich's second charge is that the social organization of medicine has a health-denying effect. He argues that medicine has turned from an attempt to enhance the healing effects of nature to endeavours to 'engineer the dreams of reason'. He quotes approvingly a criticism that oral contraceptives are an attempt to prevent a normal occurrence in healthy persons. Yet in the first section of the book he includes contraception along with smallpox vaccination and improvement of sewerage and water engineering among the items of which he approves. The charge of social iatrogenesis is a complex one. It reflects Illich's deep dislike of an industrialized and complex society. Illich ends a paragraph in which he criticizes intensive education for turning people into unemployables, intensive agriculture for destroying the subsistence farmer, and the deployment of priests undermining the community's self-control by saying that 'the malignant spread of medicine has comparable results'. Yet, despite Illich's charge, medicine did not invent disease. Healers of various sorts have exercised great influence amongst most communities because they were the only individuals to offer any hope for the relief of suffering derived from disease. The rise in influence of modern healers must have something to do with the fact that almost for the first time they have effective treatments in their hands. It is difficult to avoid the opinion that Illich resents medicine to an extent which is quite irrational. Nowhere is this more obvious than when he writes about the relief of pain under the heading 'The Killing of Pain'. Among the virtues that he claims enable people to resist pain with fortitude are patience, forbearance, courage, resignation, self-control, perseverance, meekness, duty, love, fascination, routines, prayer, and compassion. He claims that pain is part of a man's experience of a marred universe and its meaning is cosmic and mythical not individual and technical. It is a sign of corruption in nature and man is a part of that natural whole. Illich believes that much of modern pain is man-made. Yet pain in the sense that most people understand it, the pain of childbirth, a sprained or broken limb, abdominal colic, an inflamed ear or tooth has not been caused by society and must have been more common in

earlier times than it is today. One of the most precious gifts of medicine is the ability to relieve severe pain. The relief of the pain of a child with a broken limb or an old man with a myocardial infarction by morphia is both dramatic and beneficial. Pain was not invented by the philosophers and most people would not find Illich's arguments very convincing. When he argues that pain-killing makes people into unfeeling spectators of their own decaying cells, I wonder if he has ever witnessed the depersonalizing and socially isolating effect of chronic severe pain and the reintegration and restoration of personality that is possible in that same individual, if pain is effectively and continually relieved.

In his fourth section on the politics of health, Illich charges medicine in general and medical science in particular with counter-productivity. He claims that by turning from art to science, physicians have lost the beneficial traits of a guild of craftsmen employing empirical rules as masters of a traditional practical art. By tortuous argument, he decides that the better the patient can be controlled, the more predictable will be the outcome of a medical encounter, the more predictable the outcome on a population basis, the more effective will the organization appear to be. He believes that the technocrats of medicine promote the interests of science rather than the needs of society. This argument ignores two important considerations. First, experimental medicine does lead to more effective forms of management and treatment. Any increased influence that its practitioners thereby enjoy can be said to be in part deserved. Secondly, that much of the challenge and interest of medicine lies in the very heterogeneity of human genetic, environmental, and cultural make-up and response, and most medical scientists are much more interested in understanding and accommodating themselves to it than trying to eliminate it. But to Illich the encounter between doctor and patient is much more of a priestly matter than a scientific one. And, of course, he is half right. Human contact and human sympathy is very important to the sick but human contact and warmth combined with the effective decisions and treatment are worth far more than when the sympathy is combined with random and ineffective advice. Illich should not argue (although he does!) on the one hand for empiricism and on the other launch salvoes against misdiagnosis

and mismanagement. However, one of the attractions of Illich's writing is how rarely he resists the temptation to fire his guns, in both directions, if they are primed with inflammatory sentences.

Illich concludes his book with a sentence 'medical nemesis is a negative feedback of a social organisation that sets out to improve and equalise the opportunity of each man to autonomy and ended by destroying it'. Unfortunately, mankind is not so perfectly adapted to a benign environment and there is no way that an over-populated earth can turn back the clock to a hunter-gatherer's Eden.

The best refutation of the charge that the medical care system is a doctor-inspired conspiracy comes from the bibliography of Illich's own book. Many of his quotations are from the writings of doctors who themselves are critical of different aspects of medical care and are seeking to improve it. No doubt it suits Illich's argument to ignore medicine's own efforts to improve the quality of the performance of its practitioners, because it tends to invalidate some of his charges against the medical profession and, if it succeeds, would make it more difficult to break the system. However, if Illich is wrong about the present, he may not be necessarily wrong about the future. Horrobin who wrote an answer to Illich's book concluded that 'all trends suggest that things will degenerate progressively and that Illich's faulty description of the present may not be far wrong as a true account of the future'. This gloomy prophecy could only come true if the self-criticism and self-regulation of medical care was as ineffective and uncritical in the future as it has sometimes been in the past. I believe that there are grounds for hope that we shall do better in these matters as the need for better evidence of efficacy and quality in medical care becomes more widely accepted.

CALLOUSNESS

New methods of diagnosis and treatment are developed by experiment in man. In this sense experiment means the use of a procedure that is not part of accepted good clinical practice or omission of one that is. Such experiments range from carefully designed research protocols to decisions of individual physicians

and surgeons. Examples of the second kind include the first closed mitral valvotomy by Henry Souttar in 1925 and the cardiac catheterization by Werner Forssmann in 1929 (on himself). Experiments in man necessarily involve some risk, although this is usually very small. Hugh McLeave (5) wrote a popular account of the development of modern surgical techniques entitled *The Risk Takers*. McLeave meant that the surgeons were the ones taking the risks. The surgeons may have indeed risked their reputations, but the patients risked something more.

Modern medical experimentation evolved slowly. Physicians and surgeons were not trained in the design of experiments. Most experiments in man arose because doctors were confronted with patients with serious conditions for which there was no effective form of treatment. In these circumstances anything which seemed to hold out a hope of improvement seemed justified, even if the risks were unknown. It was in this spirit that procedures like cardiac surgery and renal dialysis were developed. However, once a form of treatment had been developed which was judged to be effective, the risk-to-benefit equation with the next development clearly had to be subjected to a more critical appraisal.

Deliberate experimentation in man expanded considerably in the 1950s and 1960s and so did the criticism of the ethics of what was being done. This criticism took two main forms. The first was that new forms of diagnosis and treatment were being developed on patients to whose care they might be relevant but who were given no proper explanation of the aims or risks of the procedures involved. The second, and more serious, charge was that experimental physiology was being conducted on patients with objectives that were irrelevant to their individual care and without their knowledge or consent. Concern about the ethics of human experiment culminated in a book by Dr M. H. Pappworth called *Human Guinea Pigs* (2). In this book Dr Pappworth compared the ethics of some medical experiments with those carried out by doctors on the inmates of concentration camps in Nazi Germany. He was particularly critical of procedures which involved arterial catheterization or biopsy by needle. Even in the eleven years since the book was written, many of the procedures that were criticized have become standard clinical practice. The

book devoted several pages to the hazards of coronary angiography and included the following remarks: 'In most series dealing with coronary angiography, the actual numbers of patients for whom surgery has been seriously contemplated must have been very few. Certainly the patients should be informed of the high mortality rate and poor results of such surgery.' Since those words were written, coronary angiography and by-pass surgery have become a health industry in their own right and there is some, although admittedly scanty, evidence that certain categories of patients with left main stem disease have an improved life expectancy as a result of by-pass grafts.

Pappworth argued that the protection afforded to patients by existing procedures in hospital was insufficient and that unless the medical profession stopped unethical practices, a public outcry would eventually cause opposition to all medical research. In fact, he took the argument much further and called for legislation and a public inquiry by Parliament because he was unconvinced of the effectiveness of ethical committees whose membership was entirely made up of doctors working in teaching hospitals. Such committees were already coming into being, under pressure from the MRC, before *Human Guinea Pigs* was published but there is little doubt that the book and the subsequent debate gave the movement a powerful impetus. All institutions undertaking research on human subjects in Great Britain now possess an ethics committee whose function is to scrutinize all proposals for research in man. They usually receive a written submission from the investigator setting out his objectives and the technique to be used. A statement about the risk of the procedure will be included and it is also a common practice to require that the investigator submit for approval a statement concerning the aims, procedure, and risk couched in simple terms that will be given to each volunteer at the time consent is sought. That consent will be recorded in writing.

Most ethical committees have expanded their membership to include lay people and all exclude anyone directly concerned with the research project under discussion. The present system seems to be a reasonable compromise between the need to protect and inform the volunteer and the desire to avoid a complex

bureaucratic mechanism which would slow down worth-while research.

Most ethics committee decisions follow closely the principles promulgated by the World Health Association in the Declaration of Helsinki in 1964. This laid down that clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject. Clinical research should be conducted only by properly qualified people and after appropriate preliminary laboratory and animal experiments. Such research on a human being could only be undertaken with his free consent after he had been fully informed. Consent should as a rule be obtained in writing.

While I think it is fair to rebut the charge of callous and unethical behaviour levelled against clinical research workers, there is one aspect that was not raised in Dr Pappworth's book that still gives me cause for concern. What happens if something goes wrong? Although serious mishaps causing irreversible harm or death are very uncommon, they do occur and one or two such episodes have been recorded in the literature. What happens if something does go wrong and an individual is permanently harmed or even killed? If the experimental team has been negligent, the individual or his dependents could sue them and collect damages from the investigators' malpractice insurance. The chances of such an action succeeding in Great Britain must be small, as a well-organized research unit goes to great lengths to ensure a high standard of technical competence and this should enable them to rebut a charge of negligence. Otherwise the subject can only look to the normal provisions of Social Security and possibly an *ex-gratia* payment from the sponsor of the research. The need for some scheme of insurance for volunteers who take part in clinical research has been argued on many occasions. Such research should not be carried out unless it is in the general interest. If it is in the general interest, the subjects are carrying out a public service and should not have to suffer financial loss if there is a mishap. It is possible to obtain commercial insurance for normal people who take part in experiments, although the premiums are high. Insurance companies argue that they can assess the risk of a healthy person dying or suffering serious illness

over a defined period of time and therefore can assess the likely maximum extent of their liability. They will not, however, insure patients with disease. The explanation for this attitude lies in the nature of the insurance provision. It is the essence of such insurance that a payment will be made if there is a reasonable likelihood that the experiment was responsible for the harm the patient suffered. It may be very difficult to be certain and so a worth-while scheme of insurance must err on the side of generosity with an arbitration procedure. Suppose a new form of treatment is being tried in patients who suffer a condition in which there is a mortality of 5 per cent per year. Suppose, too, that the new treatment is to be tried out in 100 patients and that the period of insurance would be for one year after the treatment began, each individual being insured for £40,000. If the treatment were completely ineffective, 5 of the 100 in the active treatment group might die. If all the dependants were to argue that there were grounds for supposing that the treatment might be responsible for their relative's death, the insurance company would have a liability of £200,000. To allow themselves a margin of profit, they might feel it necessary to charge a premium of £3,000–4,000 per patient insured per year and no research supporting organization, public or private, would pay such a premium. Thus, an individual approached to take part in a clinical research project which involves anything more than a trivial risk might be acting in his own best interests by declining. As an individual he has nothing to gain and he might have something to lose. On the other hand, the progress of medicine would be halted were it not for the public spirit of those who agreed to take part in research as subjects. In truth the risks are very small and in most cases are more than counter-balanced by the exceptionally high standard of care offered to patients taking part in research procedures and clinical trials. These people deserve our honour and respect but, in my view, they also deserve an *ex-gratia* scheme of compensation, even if the standards of proof of cause and effect for compensated mishaps were to be set fairly high.

IRRELEVANCE

The Rock Carling monograph by Professor Thomas McKeown (3) was the culmination of a formidable life of scholarship. He was one of my teachers as a medical student and I have a great admiration for him. In the monograph, McKeown argued that by far the greater part of the improvement in life expectancy over the past 150 years had been due to improvements in sanitation, housing, and nutrition and that the role of medicine and medical science had been minor. He based his arguments upon his analysis of changes in over-all life expectancy and deaths from specific causes. He showed that mortality from most infectious diseases had begun to fall before the general introduction of antibacterial chemotherapy and suggested that the contribution of antibiotics had been very small. The facts are not in serious dispute. I accept the thesis that sanitation, clean and abundant food, and better housing has made a great contribution to health, but I dispute the conclusion that these have been the main factors at work in the last thirty-five years.

McKeown bases his conclusions almost entirely upon mortality. He does so on the grounds that the figures are available and reliable. He extrapolates trends in mortality over long periods in the past into the present and thus assumes that deviations from these trends are an accurate measure of the effect of medical interventions. The justification for doing this even with infectious diseases such as tuberculosis seems debatable. Notifications of pulmonary tuberculosis fell in an almost linear fashion between 1915 and 1939. Thereafter, they rose until 1953, when the number of reports was still above the 1939 value. Extrapolation of the 1915–39 trend line of reports of respiratory tuberculosis would have suggested that there would have been only 41 per cent as many cases as, in fact, there were (6). McKeown, who extrapolated the mortality figures over this period suggested that 51 per cent of deaths were prevented by 'streptomycin'. If one assumes that the case fatality rate was unaffected by measures taken prior to the introduction of chemotherapy, McKeown's calculations must seriously underestimate the contribution of drug therapy.

Projections of data outside the limits of measurement must always be treated with caution. Referees of scientific journals automatically strike out conclusions based upon such insecure grounds. A calculation made on the basis of the increase in the number of horses in England during the nineteenth century suggested that if it had continued on the same trend to the present day, the country would be covered by a 6-feet layer of horse dung. Thus, such extrapolations are to be regarded as interesting contributions to a debate but not as proof of a hypothesis. Beeson (7) has pointed out that McKeown often belittles the positive achievements of medicine by coupling some constricting clause with any admission of improved medical care. For example, after suggesting that 51 per cent of the deaths from tuberculosis, that would have occurred after the introduction of chemotherapy, were prevented, he goes on to say that this is only 3 per cent of all the tuberculosis deaths over 150 years in the UK. Why this negative comment, which has no relevance to the merits of chemotherapy?

It seems to be equally plausible to argue that the very substantial decline in mortality among young and middle-aged people has had a lot to do with improved medicine, especially immunization and antibiotic therapy. I cannot prove that the progressive decline in deaths associated with anaesthesia and in maternal mortality (8) are due to better medical care but I suspect that in large part they are. It seems to me very probable that the decline of deaths from stroke that began in the mid-1950s was due to widespread use of anti-hypertensive drugs, although some epidemiologists have contended that the effect is too great to be explained by the number of patients on treatment. Interpretation is rendered difficult because unexplained fluctuations in disease incidence and mortality do occur. The decline in mortality from carcinoma of the stomach which has been evident for some years is certainly not due to intervention by medical science, or to any discovery concerning the epidemiology of the disease.

From subsequent conversations with him, I know that McKeown now believes that he presented his arguments leaning too far one way to counteract the excessive claims made by medical scientists, who he felt were leaning much too far in the

other direction. So be it—but McKeown's arguments have had a wide and sympathetic hearing from reviewers, who have taken little note of the rebuttals from authors such as Beeson (7), Godber (9), and Lever (10).

DEATH IS NOT THE ONLY ENDPOINT

Thus far the argument about the irrelevance of the role of medicine has been conducted in terms of mortality. Death is dramatic. Saving life is satisfying. The media like to portray doctors and nurses in emergency situations grappling with death. It is an image that the health professions are happy to accept but it is very misleading. Most doctors spend most of their time alleviating the effects of illnesses that cause discomfort and distress but which do not imminently threaten life. Collectively these illnesses are a major burden to society and fully deserve the effort that goes into caring for them.

Musculo-skeletal disorders such as gout, rheumatoid arthritis, and osteo-arthritis of the hip are major causes of pain and disability. The effect of these conditions upon life expectancy is modest. Modern developments in the treatment of both acute and chronic gout with drugs such as indomethacin and allopurinol have made it possible to ameliorate very greatly the impact of this intensely painful and moderately disabling condition. Advances in the treatment of rheumatoid arthritis have been less dramatic. Yet the partial relief of inflammation, stiffness, and pain in the joints deformed by rheumatoid arthritis has not been a negligible contribution from the non-steroidal anti-inflammatory drugs. Osteo-arthritis of the hip is a chronic disabling and painful condition. Surgical replacement of the hip joint is extremely effective in relieving pain and in many cases produces a modest but worthwhile increase in mobility. Skin diseases form another group of uncomfortable, annoying, and inconvenient diseases that have little effect upon mortality. There is much still to be learned about treating them but steroid ointments have made a major difference to the comfort of sufferers from allergic skin rashes, especially eczema. Asthma is a more serious disease than eczema but it illustrates something of the same principle. There is no evidence that improvement in the treatment of asthma has affected

mortality, indeed between 1960 and 1967 mortality increased temporarily, probably as a result of changes in the drugs used to treat the condition. The comfort of patients with asthma and the social acceptability of their treatment has, however, been greatly facilitated by the use of inhaled steroids, cromoglycate and beta-2 sympathetic stimulant broncho-dilator aerosols. Epilepsy presents a rather similar problem. Some epileptics die from a cardiac arrest sustained due to hypoxia in status epilepticus. Others may injure themselves during fits. The main burden of epilepsy is not due to shortening of life expectancy but to the miserable insecurity of a condition that causes sudden and largely unpredictable loss of motor control. There have been worthwhile improvements in knowledge of how best to use drugs like phenytoin in control of grand mal epilepsy and also some improvements in the drugs available such as the development of sodium valpoate. A greater proportion of patients can now be maintained free of fits.

Schizophrenia does not usually bring about the death of those who suffer from it. It cannot be cured but the phenothiazines and butyrophenones have a favourable influence on many of the features of the disease and allow a reasonable degree of reintegration in society. Anxiety provoked by grief, worry, and social tension can be very disabling. The benzodiazepines are much over-prescribed but many patients with a limited period of severe anxiety are able to function better as a result of taking them.

Hernias, varicose veins, and haemorrhoids rarely cause death but they cause much distress, discomfort, and some disability. More effective means of managing them would be a useful contribution but it would not make the tiniest squiggle on the curves of mortality.

Most people expect a happy, comfortable life, free of pain and disability They do not base their major decisions upon distant prospects for life expectancy. More is the pity, because the greatest single achievement in improving health would be to persuade people to stop smoking and limit their food and alcohol intake. Much of the efforts of the medical profession and medical scientists are directed at more immediate and less ambitious objectives; reducing the pain in a swollen joint, the grief of bereavement, a urinary infection, swollen ankles from mild heart failure, etc.

Much has been done to ameliorate these with modern drugs but I agree with those who argue that these achievements are still very modest compared with what they might be. Too many drugs have an unacceptable degree of toxicity, they have to be taken too often, they do not cure the disease but only modify a symptom. It ought to be possible to improve them. The effort to find better means of treating or preventing illnesses which have little effect upon life expectancy must continue. The validity of the efforts of medicine and medical science should not be judged solely by their effects upon mortality.

THE PRICE OF REASSURANCE

It is more difficult to quantify morbidity than mortality but I believe that there are even less certain end-points that must be taken into account when judging the achievements of medicine. One of the most important of these is reassurance (11). What price does a patient put on negative information? The lump in the breast that is not cancer, the swollen lymph nodes that are not the first sign of leukaemia, the blood in the stool that is due to haemorrhoids and not to cancer, the pain in the chest that is caused by a pulled muscle and is not angina. The value of negative information in apparently healthy people appears to be very small. Screening populations to detect sub-clinical illnesses that can be treated before they become damaging has not proved to be of value (12). Many of the conditions that patients fear most are fearful precisely because treatment is well known to be unsatisfactory. Even so an increasingly sophisticated population want to know whether their signs and symptoms have an ominous meaning.

I suspect that a large part of the exponential growth of laboratory tests arises directly from a desire by doctors to expand their base of negative information. In part this may be to reassure themselves, or even those who insure them against litigation for negligence, but there are many occasions when it is useful to know that symptoms are not due to disease of the liver or kidneys, a possibility that can be rapidly excluded by simple biochemical tests. But this sort of reassurance can be a process without end until the purse is empty, and there is a need to develop a statistical basis for evaluating the usefulness of negative information in diagnosis and

reassurance. I wrote this paragraph after a brisk discussion with a highly intelligent woman doctor under my care in whom we had just found, largely as a result of her own insistence, a small second phaeochromocytoma after one had been removed from her opposite adrenal a few months before. She argued that there must be other patients with similar symptoms, who had not insisted as she had on investigation to the last ditch, in whom we were overlooking the same type of tumour. She was not impressed by my statistical approach to the problem.

Too often the search for reassurance ends in a self-defeating circle with the physician seeking to explain minor abnormalities of tests that had only a flimsy justification in the first place. But the desire to exclude serious disease is a powerful motivation amongst doctors and patients, and the glow of relief in the eyes of a patient whose fears have proved groundless provides some justification for attempting to do so. I am not sure where Professor McKeown would fit reassurance into his analysis of the role of medicine but I am convinced that it is part of the legitimate function of a doctor.

THE QUALITY OF LIFE

There have been few attempts to measure the effects of medical interventions upon the quality of life but it is a matter that assumes increasing importance as long-term treatment becomes commonplace. Often the decision to develop a new form of treatment is that it will place a smaller burden of side-effects upon patients than the present standard form of therapy. One of the great problems is the measurement of disability and symptoms and the comparison of unlike quantities. I am doubtful if it will ever be possible to use a single monetary scale for this purpose, largely because of the gross non-linearity of response to small changes in chronic disability. To illustrate the point I must resort to a clinical anecdote that I think is representative. Mr X is a businessman who has angina pectoris caused by severe coronary artery disease. The severity of his symptoms varies but in cold weather he is often halted after walking only 30–50 yards. The nearest shops and bus stops are about 400 yards away so that on a bad day he must halt several times on his way to them which he finds embarrassing and infuriating. On treatment with propranolol and isosorbide he can

manage about 250 yards on a bad day before he has to halt. He regards this as an enormous improvement in the quality of his life because he can now do most of the things he wants to do without stopping. On an absolute scale it is a miniscule improvement. A healthy man of his age should be able to walk several miles without stopping and the difference between 50 and 250 yards would be barely visible at one end of the scale of capacity. The answer is that the horizon of this man had been reset by his disability to about 50 yards. The gain of going from 50 to 250 yards was not a factor of five but almost infinite because it gave him back access to the world. To regain the capability of carrying out some commonplace task which illness had removed from their grasp seems to me as an observer of sick people to be something much more valuable to them than one would guess against the background of the absolute range of possible achievement.

CREDULITY

While I reject the charges of conspiracy, callousness, and irrelevance laid against medical practitioners, I find it very much more difficult to resist the charge of uncritical over-enthusiasm.

A lack of self-criticism and insight is altogether too common amongst clinical investigators, especially those involved in procedures that might seem particularly in need of cautious evaluation. It is not difficult to understand how this situation has come about.

Patients often come to their doctors in search of hope and they usually find it. While attitudes about patient information concerning diagnoses have changed, so that it is now rare to conceal a serious diagnosis from a patient, it is still commonplace to give a much more optimistic prognosis than the facts justify. Most doctors defend this practice on the grounds that the clinical course of many conditions is highly variable and thus it is reasonable to hold out to the patient the hope that his illness will follow the most favourable rather than average course. Furthermore, it is easier to persuade a patient to follow a course of treatment if the therapist exudes confidence in the correctness of his advice and the favourable nature of the likely outcome. Those of us who are tormented by scientific doubts almost certainly are less effective

therapists than those who are confidently unaware of their own ignorance, or choose to conceal it. As they purvey their messages of hope, doctors rest much of their confidence upon two factors, largely outside their control. These are the self-limiting nature of many diseases and the placebo effect.

A great many consultations with doctors are produced by symptoms whose natural course is either to improve or at least to fluctuate. Most feverish colds, bouts of diarrhoea, aches and pains in muscles and joints tend to get better without medical intervention of a specific kind. More serious conditions such as angina pectoris or intermittent claudication have a tendency to undergo spontaneous improvement. In an illness which runs a fluctuant course the patient is most likely to seek medical assistance when his symptoms are at their worst. When he is seen on another occasion chance suggests that he is likely to be somewhat better. Statisticians term this phenomenon 'regression upon the mean'. Practically any treatment may look good under such circumstances and the great variety of nostrums that have been advocated in good faith for the treatment of multiple sclerosis is an eloquent testimony to this.

The placebo effect is also a powerful one. It is particularly evident in the relief of pain and in minor disorders of mood but it is of some significance in all illnesses, even terminal cancer. Many studies have shown that inactive substances are quite effective in relieving pain such as that occurring after a surgical incision or that caused by ischaemic heart disease. The relief of pain is less on average than that given by a powerful active drug such as morphia but it is common for half the patients with pain to respond to a placebo. The power of suggestion in the placebo effect is well illustrated by the ability of surgeons in China to carry out superficial operations under 'acupuncture anaesthesia'. The effects of placebos upon mood has been studied in a number of circumstances. One of these is a class experiment with medical students when red and blue tablets containing lactose are given, accompanied by the suggestion that the tablets contain an active drug which may alter mood. On average the students who receive the red tablets notice a mild euphoriant effect, while those that receive the blue tablets note depression. The popularity of various

medicines for patients with terminal cancer is also to be explained on the same basis. Laetrile is only the latest in a long succession of substances that have brought comfort and improvement in well-being to patients who feel they have been abandoned by the medical profession because of their bad prognosis. Laetrile has at least the advantage that it does not cause serious toxicity.

The general public, politicians, and many doctors underestimate placebo effects and tend to assume that a medicine that obviously makes somebody feel better must have a powerful active ingredient. The powerful active ingredient is there but it is the suggestion that accompanies the medicine rather than the chemical constituents of the pill.

The reputation and success of many healers rests to a large extent upon natural recuperation and the powers of suggestion. To these must be added a third important source, the differential effect of memory for favourable and unfavourable events.

Doctors, being human, and dealing every day with the problems of other humans, tend to be disproportionately influenced by their own experience, rather than the general experience of the disease conditions which they treat. In the short term both favourable and unfavourable events can have a powerful effect upon their behaviour. It is difficult to repeat a procedure, even if it seems eminently well justified, if only a few days before a patient has suffered serious harm or even death as a result of it. It is even more difficult to resist the temptation to repeat a recent success even if the indications for it are much less clear than they were in the successful case. In the long term, fading memory of the failures but an evergreen recall of the successes seems to influence many doctors by persuading them that they are doing much better than is objectively the case. There are several examples in the literature, especially of surgical operations, where there is evidence of differential forgetfulness in reporting uncontrolled results of new forms of treatment. This has been evident on more than one occasion in my own field of special interests, the treatment of high blood pressure.

The main defence against these three sources of bias in the interpretation of medical intervention in disease lies in the randomized control clinical trial (RCT) for which Professor Archie Cochrane

(4) has been such a persuasive advocate. While the RCT is a powerful instrument, it has several important limitations. Such trials are often both expensive and time-consuming. They are of little use if a decision must be made quickly. The MRC trial of treatment in hypertension will probably not give a result until the mid-1980s. By that time a substantial proportion of patients who have blood pressures in the range under scrutiny in the trial may already be on drug treatment. It would be better if the result could have been available in 1975 not 1985 from the standpoint of health policy. Major issues can justify such a long delay and high cost to reach a firm conclusion, minor ones cannot. Health care sometimes undergoes a quantal change such as the jump from pneumothorax and thoracoplasty to streptomycin, isoniazid, and para-aminosalicyclic acid in the treatment of tuberculosis. This is a suitable subject for a major outcome trial. Often the changes are incremental and each step is relatively minor in itself. It is very hard to decide the correct time to freeze two types of practice and carry out a full randomized controlled comparison of them. Yet the lessons of the randomized controlled trial can often be applied when the full rigour of the technique cannot. Every doctor who is engaged in the study of new methods of care must be aware of the likelihood of bias both in case selection and in evaluation of outcome.

When leading clinical research workers show themselves to be credulous optimists, what hope is there for the rest of the profession? Experience with intensive coronary care is an object lesson. Claims were made in good faith that intensive care halved mortality. Two randomized controlled trials have failed to show any difference between patients looked after at home and those admitted to a hospital intensive care unit (13, 14). The claims based on uncontrolled studies must have arisen as a result of changes in case selection. Well-trained research workers still make elementary blunders based on inadequate case selection and bad experimental design. An example may be in order. The concentration of the sympathetic neurotransmitter, noradrenaline, can be measured in plasma and used as an indicator of the level of activity in the sympathetic nervous system. Anxiety and fear is one factor that can increase such activity. Early studies of plasma noradrenaline in

relation to level of blood pressure showed a positive relationship suggesting that increased sympathetic activity might play a causal role in chronic hypertension. Further investigation showed that the normotensives included in such investigations were laboratory personnel well used to the procedure, while the patients were not. When the observations were repeated with both normotensives and hypertensives coming from a population sample who did not know their blood pressure in advance and were not used to the procedure, there was no difference in their plasma concentrations of noradrenaline.

Before writing off clinical research workers altogether, Professors Cochrane and McKeown might investigate the beneficial effect of teaching them some epidemiology. Human populations are a worthier subject for proper experimental studies than are colonies of rats.

TECHNOLOGICAL INHUMANITY AND THE POSTPONEMENT OF DEATH

To die with comfort and dignity is a reasonable human aspiration that is not always achieved. The charge is made, sometimes with reason, that doctors strive officiously to keep alive individuals who are past hope and should be left in comfort to die as speedily as nature will allow. This dilemma embodies a basic conflict which can be illustrated by the current attitude to two pieces of technological hardware, the respirator and the artificial kidney. In the current folklore the former is bad and the latter good. Parents go to court to try and obtain authority to turn off respirators on their hopelessly brain-damaged children. Street collections are organized to buy an artificial kidney for a neighbourhood resident who is dying of renal failure. Obviously the major difference is the hope of a reasonably independent existence but at the time artificial support of life is initiated, it can be very difficult to know whether the decision will prove to have been wise. If it turns out that the situation is irrecoverable, it is not simply a question of changing course but of making a complete reversal of policy from all-out attempts to bring about recovery to withdrawal of all active means of trying to sustain life. As one cannot change one's

mind about the wisdom of the decision after the patient is dead, the temptation is strong to temporize and keep the patient alive until all hope is spent.

I believe that two and possibly three separate concerns have become intermingled in the concern about artificial support of life. The first is the physical and mental fear of being treated like a mindless piece of meat, while multiple intravenous lines run into the body and machines take over many of the functions involved in the maintenance of life. An intensive care unit after major cardiac surgery is much like that. The only justification for the methods is the outcome. There is little doubt that such drastic interventions as replacement of heart valves or total correction of major cardiac congenital abnormalities could not be undertaken without the armoury of electronic pacemakers, respirators, monitors for blood pressure and heart rate, infusion pumps, etc. I share the public concern. Indeed, I am not keen ever to see myself in the middle of this web of machines but, if they offered the hope of preventing early death or major disability, I have no doubt that I should accept it with something approximating to the same stoicism that most patients do. There is no alternative.

If the dehumanizing effect of the intensive care unit is in large part unavoidable, the same cannot be said for other contacts with technology. Even something as simple as an electrocardiograph or a chest radiograph is frightening for a few people. How much more frightening is a barium meal or a course of radiotherapy? Doctors, nurses, and radiographers and other health personnel vary greatly in the attempts they make to allay fears and their understanding of the level of sophistication that is appropriate for their explanations. Patients neither appreciate being talked down to, nor being faced with technical words whose meaning they do not understand. It is, in part, inevitable that the machine becomes the central focus of many technological encounters, because if the machine does not do its job the patient's time will have been wasted and perhaps even their safety put at hazard. Much more could be done to allay anxiety by taking people to see machines before they are used and by giving them a commentary on progress of the procedure but it needs time and staff training and these are often not forthcoming.

The greatest fears seem to be aroused by technological encounters of the third kind: suspended animation or the postponement of death when the brain has died or any kind of worth-while existence is clearly no longer possible. Paradoxically, the most difficult problems are not those that have received most publicity. There are reasonably satisfactory electroencephalographic, angiographic, and biochemical means of determining if the brain is damaged beyond all hope of recovery. Turning off a respirator under such conditions tugs at the heart strings but it is not a very difficult decision and it is usually taken collectively by all the doctors responsible. Much more difficult are the marginal decisions in the elderly. An old patient previously well is admitted immediately after a stroke. Paralysis is extensive but the immediate course is unpredictable. Down goes a nasogastric tube to administer fluid and nutriments. A bladder catheter to prevent painful distension and the skin deterioration that will occur from lying in urine-soaked bedclothes. Nurses will turn the patient at frequent intervals to prevent bedsores. A ripple blanket begins to whir away for the same purpose. Physiotherapists put the paralysed limbs through passive movements to prevent contractures. A chest infection and a urinary infection supervene and appropriate antibiotics are given. If all is well, the patient may recover rapidly and, if he or she is very fortunate, get back on their feet with only moderate long-term disability. Often there is not a great deal of recovery. The patient is dysphasic and cannot communicate properly with the nurses and doctors. After some degree of early improvement, the situation begins to deteriorate again. Bedsores appear and deepen. The chest infection gets worse. At some stage the consultant in charge and the ward sister will decide it is time to call a halt. But they usually give the patient the benefit of a lot of doubt before they do so. All active measures are stopped but which are the active measures? Do you pull up the nasogastric tube and let the patient die of dehydration? Pull out the catheter and let them soak in urine? Stop the antibiotics and risk the health of staff and patients with volumes of purulent sputum? Stop turning the patient and let the bedsores worsen? In practice, most of these things are continued, except possibly the antibiotics, and such is the resilience of the body, the patient for whom all hope

has been abandoned may be a long time dying. Very, very occasionally they may improve so much after this decision has been taken that active measures have to be re-instituted.

It is often not a pleasant spectacle, particularly for the relatives who see the last agonies of their nearest and dearest, unprepared by the professional training of the doctors and nurses. The best that can be said is that most such patients can be and are kept free of severe pain. Stupor and coma draw a curtain across the mind of the dying but do not hide their disintegration from the living.

APPLICATION TO REALITY? THE LIMITATIONS OF SCIENCE

Should we emulate past practices in China and require our scientists in the MRC Laboratory of Molecular Biology to spend a month or two each year working in a geriatric hospital to see what they can do to help old people with dementia or incontinence? I imagine that even the suggestion would being a smile to many scientists' faces and a vigorous volley of letters to the newspapers if it looked like a serious proposal. Yet, that in many ways is what is being asked when it is urged that less money should be spent upon basic science and more upon applied. Direction of labour may not be considered politic in these days of union power but direction of resources has much the same effect.

I shall have much more to say about the unity of scientific research when I turn to the positive role of science in discovery of new forms of treatment but at this stage I intend only to raise the fundamental limitation of medical science, which is that it will always fail in the end.

Man must die. The best hope of medical science is to postpone death and maintain positive health to about the age of 80–85 in men and 85–90 in women. There is not the slightest indication that any form of social or biological intervention will radically change that situation. Too many biological clocks are slowly running down. Not only must man die but some men and women will die slowly. They are the unlucky ones. Better by far a quick burst of ventricular fibrillation than a slow decay into senile

dementia and incontinence but it is not given to us to decide which shall be our fate. It was once said that everyone should be issued with a gun loaded with one bullet at birth and the wisdom to pull the trigger ten seconds before his decaying mind and body would no longer allow him to do so. I doubt if many would use it even in the unlikely event that we could arrange to give them a signal. A very great deal can be done to ease the lot of those whose mental and physical faculties are running down ravaged by time and the effects of disease. But in so far as they succeed, they only delay a problem that will recur in a different form until eventually death ends the struggle.

The contribution of science to this problem will be real but limited. The elderly develop acute illnesses like anyone else. Indeed, the majority of patients admitted to 'acute' hospitals are already over 65. As systems deteriorate they become more prone to disease. Some body systems will deteriorate at a greater pace than others. Independent existence can be prolonged by dealing with acute problems and by trying to rewind a clock whose spring seems weaker than the other parts. The treatment of depression, anxiety, grief, Parkinson's disease, heart failure, pneumonia, myxoedema, pernicious anaemia in the elderly are all in this category. But they cannot put off death, they can only try to synchronize the clocks so that the whole system becomes still more or less at the same time. This will often mean prolongation of the slow deterioration of ageing; a house that shrinks a little day by day without the roof falling in.

Medical scientists should not pretend that they can solve this problem because it is not pre-eminently medical but biological. A medical solution would be euthanasia but we have not come to that yet, officially, although one day we may. A biological solution must depend upon the action of the community. Relatively easy while the clock springs have enough tension to allow an independent, although protected existence. Very hard when they do not and some sort of institutional care must be provided. There are no high technology answers to that.

Some of the demands for more applied research have come from the desperation of policymakers, who are faced with the mounting problem of caring for the elderly. Surely those finely

tuned minds questing for Nobel prizes could do something to solve the problems if they could only tear themselves away from their intellectual pursuits? It seems to me that the answer is that they cannot and it would be misleading to pretend otherwise. Scientific methods can be used to evaluate alternative systems of care but those systems are so complex and individual that common sense and judgement might serve as well. No-one will ever emerge from a laboratory, biological, medical, or social, with a universal answer to the problem of ageing. Those who think that diversion of scientific research resources to the problems of the elderly will solve those problems are deluding themselves. Another consequence must be faced. Each success against acute illness makes it more inevitable that a proportion of the resources will one day have to be diverted from acute medical services to the social care of the elderly. That is the ultimate limitation of medical science; its greatest success would be to work itself out of a job and it will not do that by discovering the secret of immortality. But before all budding biological scientists begin to retrain as managers of homes for the elderly, I had better make it clear that I think we are decades, probably centuries away from the point when they will be made redundant. But it might be as well to recognize its inevitability in the long run.

SUMMING UP

The art of the healer has always relied to a great extent upon the natural resilience of the human body, regression upon the mean, and the placebo effect. The fall in mortality over the past 150 years must have occurred mainly because of better sanitation, agriculture, and social organization. These matters are not in serious dispute. Judged against this backcloth the role of scientific medicine is modest, but real and growing.

For those who are well, prevention offers the best hope of maintaining health, but we have much to learn about means of prevention which involve changes in individual behaviour in a free society. Those who are already ill must rely upon intervention by medical or surgical means. Advances in the understanding of human physiology and biochemistry have greatly improved the

outlook for those who suffer serious acute illness or accident, irrespective of its cause. Specific treatment has been most effective in repelling bacterial invasion of the human body. Chemotherapy of infections and a small number of surgical operations (for example, appendicectomy, ligation of a patent ductus) are the only true 'cures' that medicine can offer. But medical 'care' can prolong life (hypertension, endocrine replacement therapy), increase mobility (arthritis, Parkinson's disease), reduce discomfort (eczema, haemorrhoids, hernia), and pain (colic, angina, metastatic cancer) in a wide variety of human ills.

I see no evidence that physicians are conspiring together to promote their own interests against those of their patients. Their motives are honourable and their actions are sincere. That is not to say that their treatment is anything like as effective as they would like to believe. The path to hell is reputed to be paved with excellent intentions. While I exonerate my profession from the charge of plotting against the public I am less certain of their motives when it comes to judging their own actions. The literature of therapeutics abounds in excessively optimistic claims, many of them made by individuals with the highest professional and academic standing. If this had occurred solely by chance it should have been balanced by an equal weight of incorrect negative statements. Even allowing for the bias of scientific editors towards the preposterously positive and away from the uninvitingly negative there seems to be something to explain. Credulity is the kindest hypothesis; a touch of deceitfulness cannot be entirely excluded.

Excessive enthusiasm may also have swayed judgement in other ways. In the early days of experimental medicine, it may have lured investigators into studies that were more in the interest of science than the patient. The search for knowledge is as valid a motivation in clinical research as in the rest of science, but the subject of the curiosity must give his free consent to take part. I welcome the improved arrangements for ethical review and consent that now prevail, although the main responsibility must rest, as it always has, with the individual investigator. I believe that those who volunteer to help with medical research are performing an important public service. They have a better claim to

any public money to compensate for injury than those who suffer harm from drugs prescribed for their direct benefit.

The increasing technical complexity of encounters with doctors sometimes places a barrier between the patient and his doctor. One of the better features of medicine in Britain is that the health professions, particularly the doctors and nurses, feel a strong sense of responsibility to the patient as an individual. This feeling is not always communicated to the increasing number of others who come into contact with patients. It is a matter that deserves more attention as the NHS must at all costs retain a human face to those who use it. My expectations from science are high but they are not infinite. I see no hope of restoring dead and necrotic cells to life and thus have only modest expectations from the active treatment of heart attacks and strokes. The cells of complex organisms seem to have a design life built into them which makes malfunction and eventual death inevitable. It is conceivable that some of the specific features of ageing can be influenced by drugs but highly unlikely (and undesirable?) that the whole process can be reset. There is no scientific solution to the problem of ageing and I do not believe that there ever will be. A great many health problems in the elderly can be helped, but not the central one.

There remains a wide field of manoeuvre for medical science between a wanted cradle and an octogenarian's grave. The objective must be to secure a healthy, happy life for all within the design limits set by evolution. There is much to do and much to hope for.

VERDICT

In this section I began by propounding six charges against scientific medicine. I should like now to offer my own judgements on those charges in a highly summarized form.

Charge	*Verdict*	*Sentence*
Conspiracy	Not guilty	Discharged.
Callousness	Unproven	Improvement in recent conduct noted.
Irrelevance	Overstated	Costs shared equally by T. McKeown and the MRC.

The cases to answer

Charge	*Verdict*	*Sentence*
Gullibility	Guilty	Compulsory retraining in the design of experiments and interpretation of evidence. Forbidden to make therapeutic claims for five years.
Inhumanity	Charge withdrawn	Undertaking to improve staff training and public relations.
Lack of application to reality	Case dismissed due to lack of evidence	The DHSS prosecutor said that this was not the last that would be heard of the matter.

Thus, if the jury were to decide that the achievements of medical research are not mirage, dream, or Nemesis, as in justice it should, it is permissible to look at the workings of the research system to find its weakness and its strength. In particular, how may we best make plans and allocate resources to optimize the chance of making and exploiting useful therapeutic discoveries.

3

Planning therapeutic discoveries

Lewis Thomas in his book *The Lives of a Cell* (15) suggests that there are two ways of planning therapeutic discoveries. There is the direct frontal approach that succeeded so well with the poliomyelitis vaccines. Once it had been learnt from basic studies that there were three antigenic types of virus and that these could be grown in tissue culture, it was a certainty that a vaccine could be made. There might be doubt as to whether a killed virus or a live attenuated one would be best. These were peripheral issues, given sufficient effort success was almost guaranteed. To be sure, success required considerable organizational skill. Thomas would probably go along with Rothschild that a project of this sort must have a 90 per cent chance of success. Basic research is just the opposite. Unless there is a high degree of uncertainty it probably is not an important problem. The most important element is surprise. Thomas says that you measure the quality of the work by intensity of astonishment. The surprise may be that everything turned out exactly as predicted or the prediction may have been completely wrong and something unexpected turned up that changed the look of the problem. The chance of success in this type of work may be well under 1 per cent. But if you do not possess the basic facts required for a 90 per cent certain targeted programme, and in almost all case of important disease we do not, then those facts must be accumulated from basic research.

There is only one other source. That source is surprise from clinical research. It is a surprise that is most likely to be operative if we are exposing sick humans to a wide variety of chemical structures and watching them intently to see what happens. This was the source of many groups of active chemicals in the early days of modern drug therapy. It is a source of surprise that is somewhat less likely to operate today because the activities of government

agencies that regulate the study of new drugs make it much more expensive and time-consuming to accumulate the amount of evidence that is required before a new clinical structure can be given to man.

I believe that the reality is even more complex than Thomas's analysis would suggest. One of the problems of science is that we have been constrained by editors of journals and philosophers of scientific discovery to present things in a particular way when we all know that is not at all how it works in practice. The only way I can try and explain how complex and interdependent different events are is to try and trace through some examples. These examples are deliberately heterogeneous. I have taken two major drug discoveries of recent years, allopurinol and cimetidine. Both were highly targeted programmes, but as we shall see the target hit by allopurinol was not on the programme until very late in the day. I have taken the discovery of drugs to treat hypertension as a result not of targeted programmes but of clinical surprise. My examples from clinical research in the strict sense are also difficult to classify. Fluid replacement therapy was gradually improved by an iterative approach without a single breakthrough discovery. Yet the end result has been highly satisfactory compared with what went before. Oxygen therapy could have been an example of a targeted programme in the hands of clinical scientists. In a sense it was, but the iterative technique was well to the fore, as problems prompted solutions which created new problems to which solutions were found. Finally I have a word to say about the contribution of technology, chiefly because I think it has quite unfairly been made the main target of those who are frustrated with the cost and organization of the medical care system.

After recounting these case histories I shall try to draw together the lessons that can be learnt from them. I hope that most of them will be obvious.

ALLOPURINOL IN GOUT

Allopurinol is a drug used to prevent gout because it partly inhibits the formation of uric acid in the body. Its discovery was a 'surprise' but Dr George Hitchings who recognized the surprise as a potential therapeutic breakthrough in gout happens to be one of

the two greatest living discoverers of new therapeutic compounds. Amongst many other lessons it shows that a 'surprise' needs a prepared mind to recognize it for what it is. Many different lines of research converged to make this discovery possible. The first of these was the clinical definition of gout and the second was the discovery of its relationship to uric acid.

Hippocrates described the main features of gouty arthritis. He termed them podagra, chieragra, and gonagra, depending upon whether the toe, wrist, or knee was chiefly involved. Galen thought that the disease was caused by unnatural accumulation of matters in the involved joint. Rodulfe in the thirteenth century is credited with naming the disease from the French 'goutte'. The seventeenth-century English physician, Sydenham, gave what still remains one of the best clinical accounts in his treatise on gout.

Uric acid was discovered as a component of human urine in 1776 by Scheele and almost simultaneously in bladder stones by Bergmann. Its role in gout was established by Wollaston in 1797 who showed that the chalky stones that accumulated in gouty joints were mainly composed of this substance. Garrod followed up this observation in 1847 by showing raised concentration of uric acid in the blood of gouty patients. Almost the only major contribution to the clinical features in recent times has been the discovery of the role of white cells in phagocytosing uric acid crystals and setting off the inflammatory response.

Progress in prevention and treatment of gout was much slower. Perhaps the best advice came from Alexander of Tralles, a Greek physician writing in AD 580 who recommended little meat, strict temperance, bleeding, and purging with colchicine, a substance obtained from the corm and seeds of a lily that grew near the town of Colchis in Asia. This advice was not to be bettered for another 1,300 years, but neither was it universally accepted. Duckworth's treatise on gout (16), published in London in 1889, devoted over 100 pages to treatment. Twenty of them were devoted to hydrotherapy with a detailed account of the composition and virtues of individual mineral springs. He also advocated physiotherapy and quoted an adage that 'no man need have the gout who could afford a slave to rub him'. The one

useful measure was his firm recommendation of colchicine for the acute attack although he looked upon it primarily as a purgative and advised that it should not be given until the attack was well advanced. Otherwise there was a great deal of nonsense about good diet and wine, castor oil, euonymin, calomel, and wintering in Algeria (Egypt was too relaxing). To be fair Duckworth gave his multiple prescriptions with little conviction. He had to recommend something for a painful and recurrent condition even if in his heart he knew that these measures were ineffective.

Meanwhile some distant advances in chemistry were laying the foundations for future progress although it is not likely that a mission-orientated research programme on gout in the late nineteenth century would have spared them a passing glance. This work involved the chemical analysis of material isolated from bladder stones, guano, heart, spleen, and pancreas. These substances were the purine nucleotides. Marcet separated xanthine from urinary calculi in 1817 and Unger isolated guanine from guano in 1846. Hypoxanthine was discovered in heart and spleen tissue by Scherer in 1850 but adenine, the last of the physiologically important purines was not discovered until 1885 by Kossel in pancreatic tissue. The great German organic chemist, Emil Fischer showed that all of these, and uric acid, have a common ring structure. The relationship of the purines to nucleic acids began with the work of Miescher in 1871 who isolated a substance he called nuclein from pus cells and later from the spermatic fluid of the salmon. Nucleins were found to be a universal component of cell nuclei. Kossel hydrolysed nucleic acids and isolated the purine bases from them. Thus the source of uric acid from nucleic acid metabolism was discovered by 1888 (17). Folin writing from the McLeod Hospital for the Insane in Waverley, Massachusetts, in 1905 showed that nucleic acid breakdown responsible for the formation of uric acid came partly from food and partly from breakdown of endogenous nucleic acid. Thus the advice of Alexander of Tralles to limit protein-rich food was partly vindicated. Later work was to show that uric acid excretion is retarded when ketones are being excreted. As consumption of alcoholic beverages is the most common cause of recurrent ketosis another aspect of his advice was found to be soundly based.

Meanwhile an advance in the treatment of gout was to come from the need to conserve precious supplies of penicillin in the late 1940s. Penicillin is actively secreted by the renal tubules and if this path is blocked the time of retention in the body can be prolonged. Carinamide, was found to be capable of blocking penicillin transport in the renal tubules, but large and frequent doses were needed. Probenecid was introduced as a development of this type of action and although it has since been abandoned as an adjunct of penicillin therapy, it was found to increase renal excretion of uric acid by preventing its reabsorption in the renal tubules. This was the first drug that was effective in the long-term prophylaxis of gout which proved capable of dispersing the deforming subcutaneous masses of uric acid in tophaceous gout. A very useful drug, it was not free from some disadvantages. It was relatively ineffective if renal function was reduced, itself quite an important cause of high levels of serum uric acid. Unless care was taken the sudden increase in the amounts of uric acid in the urine could cause crystal formation in the renal tubules and impairment of renal function. There was a high incidence of skin rashes. The story switched back again to the purines.

Once the essential nature of purine bases as building blocks of nucleic acids was known (and long before their importance in the genetic code was recognized) attempts began to damage rapidly dividing malignant cells by using chemical analogues of the purines. One of these substances was 6 mercapto-purine tested along with thioguanine in 1951 by Hitchings and Elion, working at Burroughs-Wellcome in the USA. They wrote that the programme had been initiated for the insights it would give into nucleic acid metabolism and because it appeared probable that new chemotherapeutic agents would result. In its first animal tests 6 mercapto-purine gave negative results for anti-tumour activity, but later results were positive and the drug was taken into clinical trial in 1952. Several hundred purine analogues were made in this research programme, among them some with a pyrazole ring in which the position of a nitrogen and carbon atom were reversed from the natural ring. The guanine analogue of this structure proved to be hepatoxic and the adenine derivative (4 hydroxy-pyrazolo-(3,4d) pyrimidine) appeared at first to be biologically

inert. These substances were later found to be potent inhibitors of the enzyme xanthine oxidase which degrades xanthine to uric acid. This enzyme is also responsible for oxidizing the anti-tumour agent 6-mercaptopurine (6 MP) to 6-thiouric acid and thus inactivating it. Hitchings and Elion decided to use it to potentiate the action of 6MP by slowing its metabolic breakdown, and it was quite effective for this purpose. However, much more interestingly it proved to be a highly potent drug for lowering the concentration of uric acid in the blood and they went on at once to develop it as a therapeutic agent for gout (18). Allopurinol in clinical doses reduces the body production of uric acid to about half the pre-treatment value and its action is independent of the state of renal function. Once the body pool of uric acid has been depleted attacks of acute gout become very rare although their frequency may be increased while crystals and tophi are dissolving and being removed. Allopurinol has become the preferred agent for the long-term management of gout (19). Treatment is not accompanied by any risk of uric acid crystals in urine because the amount excreted is reduced. Possible concerns about the adverse effects of inhibiting an important enzyme were in large part allayed because the enzyme is deficient in the disease xanthinuria and this is not associated with very serious consequences.

CIMETIDINE FOR PEPTIC ULCER

Cimetidine is a drug that reduces the output of acid in the stomach by inhibiting a gastric receptor for histamine. It was discovered by a team led by Dr James Black (20) and it is the nearest approach to a deliberately targeted programme of any that I shall illustrate, but it is very doubtful if any members of the team would have given themselves anything approaching a 90 per cent chance of success when they began. When they set out, the central role of histamine in the control of gastric acid secretion was still controversial. By discovering cimetidine and other similar compounds they not only discovered a new class of therapeutic agents but they proved a physiological hypothesis.

Before an attack on peptic ulcer via inhibition of gastric acid secretion could be made it was necessary to appreciate that the

stomach secreted acid, that increased acidity had something to do with the causation of duodenal ulcer and to know how acid secretion is controlled. The groundwork of this knowledge began to be assembled over 200 years ago. Réaumur (1752) and Spallazani (1783) lowered perforated capsules into the stomachs of various species of animals and recovered them by means of attached strings or by causing vomiting. Using these methods they showed that gastric juice is acid and will digest food *in vitro*. Seventy-two years later chemical methods were used by Prout (1824), and Tiedmann and Gmelin (1824) to show that the acid concerned was hydrochloric acid. Beaumont (1833) was the first person to make systematic use of a human patient with a gastric fistula to study the processes controlling gastric secretion. His famous patient, Alexis St Martin, enabled him to show that emotion and the sight of food could change the vascularity of the gastric mucosa and the flow of gastric juice. He obtained pure gastric juice but made only limited chemical studies on it. However, these suggested that hydrochloric acid was not the only substance able to digest food which was present in it. The other main component, pepsin, was discovered by Wassman in 1839. Experimental physiologists began to make extensive use of animals with gastrostomies and Bidder and Schmidt showed that the hydrochloric acid was secreted by gastric glands. Invention of the technique for isolating a pouch of stomach wall by Heidenhain (1878) and further improvement in the technique so that the nerve supply remained intact by his pupil Pavlov, gave a powerful impetus to experimental work on gastric secretion. The introduction of soft flexible catheters for repeated sampling of gastric juice in man gave a similar push to human research in the 1912–16 period.

Pavlov and his associates working in St Petersburg in the early years of the present century greatly extended knowledge of the control of gastric secretion. They established, using sham feeding experiments, that the sight or ingestion of food could stimulate the flow of acid juice in the stomach. Using isolated pouches of gastric tissue they were able to show that this was mediated by the vagus nerve because denervation of these pouches reduced the flow by 80 per cent or more. The existence of local mechanisms

for stimulating the flow of gastric juice was for long a source of bitter controversy. Edkins (1906) thought he had demonstrated a specific secretagogue in the pyloric mucosa. His methods and conclusions were criticized by Ivy (1918) who found that meat extracts kept in contact with the pyloric mucosa for an hour had no effect upon the flow of juice from the gastric glands. The argument swung back and forth partly because no-one at that stage realized that some of the contradictory findings occurred because there were two secretagogues, histamine and gastrin.

Meanwhile clinical research workers, especially Watkinson in 1951, had demonstrated the relationship between gastric acidity and peptic ulceration. Patients with a duodenal ulcer produced more acid juice than normal subjects or patients with gastric ulcer. Energetic attempts were made with many different commercial preparations to promote the healing of duodenal ulcers by using anti-cholinergic drugs with or without antacids. Christenson, Juhl, and Tygstrup who reviewed all the randomized control trials of treatment of duodenal ulcer carried out in the decade 1964–74 came to a very gloomy conclusion. They felt that the contribution of randomized control trials to knowledge of the effect of various treatments had been rather small. The information obtained from the best randomized control trials had practically no impact upon current therapeutic practice which was predominantly based on uncontrolled observation. They noted that antacids and anti-cholinergics were being prescribed to the extent of $110 million and $60 million respectively in the USA each year despite the fact that their use had very little support from randomized control trials. The main method of treatment used in patients with severe duodenal ulceration was surgical and the principle was to sever the vagus nerve and remove a substantial part of the acid-secreting part of the stomach wall. Surgery was reasonably effective in the healing of duodenal ulcers but there was some operative mortality and considerably long-term morbidity. Patients with small stomachs experienced fullness after eating small meals and some were troubled by repeated bilious vomiting. The rapid emptying of the small stomach remnant into the small intestine produced an uncomfortable clinical syndrome which acquired its own name 'The Dumping Syndrome'. An appreciable fraction of my own

six months' experience as a house surgeon was spent in assisting at operations that were designed to refashion gastrectomies to reduce the uncomfortable symptoms the patients were suffering. In some patients, these symptoms were worse than the dyspepsia that the operation had relieved.

Attempts to regulate the flow of gastric acid by pharmacological means closely followed knowledge of the physiological control mechanisms. The vagally mediated neural control was the first to come under systematic pharmacological attack. Atropine was isolated from belladonna by Mein in 1831 and by 1867 Bezold and Bloebaum demonstrated that it blocked the cardiac effects of vagal stimulation. In 1872 Heidenhain showed that atropine prevented the secretion of saliva that followed stimulation of chordatympani. Atropine is a competitive antagonist of the neurotransmitter acetylcholine, the chemical mediator of the effects of vagal nerve stimulation. Large doses of atropine reduce the fasting secretion of hydrochloric acid in the stomach although they are less effective against the stimulating effect of food in the stomach. Many synthetic analogues of atropine have been developed and used in medicine such as propantheline. Unfortunately none of the synthetic atropine-like drugs showed any appreciable selectivity for gastro-intestinal function. They all tend to cause dryness of the mouth, blurring of vision, difficulty of micturition, and so on.

Histamine came on the scene early but its role in controlling gastric secretion was for long uncertain. The synthesis of histamine was accomplished by two German chemists, Windaus and Bost, in 1907 and its pharmacological properties were extensively studied by Dale and Laidlaw in 1910. It proved very difficult to establish whether or not histamine was a natural hormone or transmitter substance. Extracts of many tissues contained histamine, especially if these had undergone autolysis or bacterial decomposition and many research workers doubted whether histamine was present in normal living tissues. Abel and Kubota isolated crystals of histamine from extracts of fresh stomach tissue of the dog in 1919, but doubt still lingered as to whether this had been presented in life or formed by decarboxylation of the amino acid histidine after death. One great source of difficulty was that

extracts of the stomach wall contained two active principals capable of stimulating the flow of acid juice, gastrin and histamine. There was a long debate as to whether 'gastrin' was or was not histamine. For example, Keeton, Koch, and Luckhardt clearly demonstrated the effects of histamine upon the flow of acid juice in the dog in 1920, but felt compelled to qualify their findings with a statement 'we do not claim that histamine has a specific stimulating effect upon gastric secretion'.

Meanwhile attention had swung away from histamine towards gastrin. Komarov, who had trained at the military medical academy at St Petersburg but worked in the USA, recognized that the acid stimulating extract of antral tissue contained a protein-like labile component. This work culminated in the isolation of heptadecapeptide gastrin by Gregory, and its synthesis by Kenner. Gastrin has a much higher activity per unit weight than histamine and many physiologists assumed that it alone was responsible for the gastric phase of acid secretion. Indeed Grossman, writing in 1967 in the *Handbook of Physiology* of the American Physiological Society stated his opinion that the hypothesis that the local release of histamine is involved in stimulation of gastric secretion was largely unproven.

In view of the potent biological activity of histamine it was clear that a drug able to antagonize its effect would be of therapeutic interest. The first progress in this direction was made by Forneau in 1937 who synthesized a series of compounds that were studied by Bovet and Staub. The resultant compounds were only weak antihistamines and were too toxic for use in man. Continuation of this line of research led to the introduction of pyrilamine maleate by Bovet in 1944 and shortly afterwards the discovery of other compounds such as diphenhydramine. These compounds inhibited the action of histamine on capillary permeability and on smooth muscles in blood vessels and bronchi. These properties led to the early antihistamines being used to treat allergic states such as hay fever. However they were generally rather disappointing and proved to be almost entirely ineffective in other allergic conditions such as asthma. The common side-effect of sedation also limited their clinical use. Drugs such as diphenhydramine have no effect upon the increase in gastric secretions stimulated by histamine.

These observations suggested that there were differences between the histamine receptors in different tissues. Ash and Schild in 1966 suggested that the histamine receptors antagonized by agents such as diphenhydramine should be termed H1 receptors and that the others should be termed H2. Black decided to develop specific antagonists of the H2 receptors and his work culminated in success in 1972 (21). A series of compounds, burimamide, metiamide, and cimetidine were synthesized. All of these drugs proved to be powerful inhibitors of gastric acid secretion. A dose of 400 mg of cimetidine given at night would render the gastric pH close to neutral, whereas without the presence of the drug in an ulcer-prone subject the pH might be around 1–2 throughout the night. Randomized controlled trials demonstrated that cimetidine was effective in accelerating the healing of duodenal ulcers (22, 23). Thus a long search for a specific and relatively safe drug to antagonize the release of acid by the stomach had eventually been crowned with success. The very efficacy of cimetidine had led to some reconsideration of the mechanisms involved in acid secretion mediated by the vagus nerve or by gastrin. It appears that histamine may act as a final common pathway in the release of acid.

DRUG TREATMENT OF HYPERTENSION

The discovery of antihypertensive drugs was a watershed because it was the first common, killing, non-infectious disease which began to yield to a pharmacological attack. Blood pressure is relatively simple to measure both in man and in animals and this fact would suggest that the search for antihypertensive drugs using animals to screen for activity would be straightforward. It is all the more remarkable that three out of the four most widely used groups of drugs to treat high blood pressure had their activity discovered in man. I have chosen this example to illustrate the importance of man as an experimental animal in drug research. As in basic research a prepared mind is prerequisite to recognize an interesting 'surprise'.

Malignant hypertension is a rare manifestation of severe elevation of blood pressure. It causes breathlessness due to pulmonary oedema, blurred vision due to retinal cotton wool spots

and rapidly progressive impairment of kidney function. The condition was identified by clinicians and pathologists such as Keith and Wagener (1939) and Volhard and Fahr (1914). Without treatment 90 per cent of patients with malignant hypertension die within a year. The recognition that much more modest elevations of blood pressure cause a considerable increase in the incidence of myocardial infarction and stroke is one of the most important achievements of epidemiology especially the study established in the town of Framingham, Massachusetts, by the National Institutes of Health. It is not my intention here to explore that aspect further or to consider in detail the evidence for the efficacy of treatment in moderate and severe hypertension. I wish to examine the discovery of the main groups of antihypertensive drugs.

In the late 1940s Paton and Zaimis investigated the pharmacology of a number of quaternary ammonium compounds and found that some of them would inhibit the effects of acetycholine in autonomic ganglia. This opened the way to lowering the blood pressure by interfering with the regulation of the calibre of blood vessels and the output of the heart through the sympathetic nervous system. The sympathetic system originates in the brain stem, relays in autonomic ganglia where acetylocholine is the neurotransmitter and terminates in nerve endings upon muscle cells in the heart and blood vessels which release another neurotransmitter, noradrenaline. The problem with blocking the autonomic ganglia was that it was bound to lead to interference with many other functions such as emptying the bowel and bladder, erection of the penis, accommodation of the eye. Smirk (1951) in New Zealand, who had many patients with malignant hypertension under his care, persevered with the use of the ganglion blocking drug hexamethonium despite these difficulties and showed that some patients certain to die in a few months without treatment, could survive for long periods. Better ganglion blocking drugs were devised but all had the same disadvantage of causing unpleasant symptoms. Drugs to blockade transmission at adrenergic nerve endings were devised at the Burroughs-Wellcome and Ciba pharmaceutical companies and these proved to be as effective at lowering the blood pressure while causing many fewer symptoms.

Drugs which directly dilated blood vessels were also discovered in animals and one of them, hydrallazine was widely used in man. Unfortunately it caused flushing and palpitations in many patients and at higher doses was toxic. Its time was to come later as a result of the discovery of the beta receptor blocking drugs.

Injective organic derivatives of mercury had been used to eliminate oedema in patients with heart failure for many years. They were discovered in man when organic materials intended for the treatment of syphilis were found to possess diuretic activity. They were rather toxic in long-term use and inconvenient because they had to be injected. Carbonic anhydrase is an enzyme that catalyses the combination of carbon dioxide and water to form carbonic acid and inhibitors of this enzyme have a weak diuretic action. Metabolic acidosis and diuresis due to inhibition of carbonic anhydrase was recognized during treatment with early antibacterial sulphonamides. Acetazolamide is a sulphonamide that was synthesized as part of a deliberate search for more potent carbonic anhydrase inhibitors. It is a fairly weak diuretic but it is active by mouth. The first benzothiadiazine diuretic, chlorothiazide, was synthesized as part of a research programme by Beyer at Merck & Co. which was designed to improve the carbonic anhydrase inhibiting action of acetazolamide. It proved to be a powerful diuretic whose action is not dependent upon inhibition of carbonic anhydrase. Chlorothiazide was introduced into medicine for the treatment of oedema, but two clinical workers, Freis in Washington DC, and Wilkins in Boston found that it also had hypotensive activity. Although it was not a powerful blood pressure lowering agent it caused few symptoms and controlled the blood pressure to a similar degree in the lying and standing positions. Both the ganglion blocking and adrenergic neurone blocking drugs caused a much greater fall in blood pressure on standing than in recumbency. Thiazide diuretics are most physicians' first choice as anti-hypertensive agents, even today twenty years after their discovery.

About two years later a chance discovery in man uncovered another type of blood pressure lowering action. Oates in Sjoerdsma's laboratory at the NIH was trying to inhibit the formation of noradrenaline in adrenergic nerve endings as a way

of reducing blood pressure. He chose alphamethyldopa, an inhibitor of dopa decarboxylase, one of the enzymes on the biosynthetic pathway of noradrenaline (24). It lowered the blood pressure to a gratifying extent and had less effect upon the blood pressure in standing position than the earlier powerful drugs. It soon became obvious that the reduction in blood pressure was not due to inhibition of dopa decarboxylase by methyldopa because more powerful inhibitors of the enzyme had little or no blood pressure lowering activity. The mode of action remained a mystery for some years. Meanwhile in Germany the Boehringer Company had a programme of research into more effective nasal decongestants. One of these made a volunteer feel weak, sleepy, and ill. It was abandoned as a nasal decongestant but one of the physicians present, Dr Wolff, suspected that some of the symptoms were due to a low blood pressure. He pursued the investigation and proved that his hypothesis was correct. After a lengthy investigation by many research workers it was established that clonidine and methyldopa both lowered the blood pressure by a similar mechanism. This involved stimulation of noradrenaline receptors of the alpha subtype, in the brain stem. Clonidine did this directly, methyldopa through its metabolite alpha-methylnoradrenaline. This was a particularly interesting type of action as it reset the brain control system rather than simply inhibiting a peripheral effector circuit.

The next major advance arose as an oblique consequence of the discovery of the beta noradrenaline receptor inhibiting action of propranolol. This drug, again discovered by a research team led by Dr Jimmy Black, had been devised to reduce heart work with the aim of treating angina. During carefully designed double blind trials of beta blocking drugs in angina, Dr Prichard of University College Hospital (25) noted that there had been a small but significant fall in blood pressure. He went on to pursue the matter in hypertensive patients and showed that propranolol had a powerful blood pressure lowering action without any difference in effect between the lying and standing position. The most widely used regimes of treatment for high blood pressure are now based on double or triple combinations which usually include a diuretic, beta receptor blocking drug and a vasodilator. A centrally acting

drug is often used where a beta-receptor blocking drug is contra-indicated. Thus, three out of the four main types of drug action now used to treat high blood pressure were first discovered to possess this action in man.

FLUID BALANCE

Modern treatment of disorders of fluid balance illustrates another important lesson. There was no sudden breakthrough. No one procedure or one brilliant investigator solved the problem. Instead a quiet persistent gnawing away at the problem developed a highly satisfactory form of therapy, most of the observations being made in the normal course of patient care. The equipment used was simple and the treatment devised relatively cheap.

The importance of the regulation of the internal chemical environment of the body was first emphasized by the great French physiologist, Claude Bernard. Loss of water and electrolytes as a result of diarrhoea and vomiting as a result of infectious gastro-enteritis is one of the most common causes of childhood mortality in the world. It is the cause of death in adults with cholera. Fluid loss is one of the main physiological disturbances in patients with diabetic hyperglycaemia who suffer an osmotic diuresis caused by heavy glycosuria. Gross disturbance of fluid balance often occurs in disease of the gastro-intestinal tract such as pyloric stenosis or peritonitis and would occur, were it not for corrective measures, after most types of abdominal surgery. Severe fluid loss causes a fall in the filling pressure of the heart, a fall in cardiac output and intense vasoconstriction which limits blood flow to vital organs like the kidney and the brain. If it is very severe, death will follow.

The principal of treating the condition is obvious. The fluid and electrolyte deficit must be replaced by a substitute of appropriate amount and composition, usually by intravenous infusion. This is not quite so easy as it sounds. Depending upon the cause and previous treatment, different types of salt and water deficit may occur. Obstruction of the oesophagus leads to a shortage of water without severe salt depletion. Diabetic hyperglycaemia leads to loss of both sodium chloride and water in about the same ratio as in plasma, accompanied by some potassium, although confusingly

the plasma potassium is slightly raised. Severe diarrhoea and vomiting may lead to loss of sodium chloride and water with substantial amounts of potassium. Both the disease and the fluid loss may cause severe disturbance of body hydrogen ion concentration which needs to be taken into account during replacement. The body is reasonably resilient about the fluid volume used for replacement, but if a gross excess is given, pulmonary oedema will result. If too much potassium is administered, the heart may stop.

Development of effective management of fluid depletion has involved many separate small developments. Two of these were technical, the development of the flame photometer and reliable autoclaves. The former made it possible to measure electrolyte composition of plasma and other fluid quickly and accurately, the latter made available a supply of sterile intravenous fluids of known composition. Improvements in intravenous equipment by the plastics industry have also made a small but important contribution to the ease of maintaining an infusion without great discomfort to the patient.

The main contribution of clinical science was to find means of estimating the deficits of different substances in fluid-depleted patients and safe ways of replacing them. The task was much more difficult if the function of the patient's kidneys was impaired for the latitude of permissible error in replacement was much smaller. A powerful impetus to improving management of such patients came in the 1939–41 bombing of major British cities. Many patients with crush injuries were admitted who had severe hypotension and renal tubular necrosis. The Bull regime of oral replacement, which included filtering vomit and re-instilling it into the stomach came from this era. Most of the research that solved the problem of fluid replacement relied upon simple methods. The volume and composition of all fluids going in and coming out was analysed so that an accurate balance sheet could be drawn up. Weigh beds were used to keep an accurate check on fluid loss of an insensible sort through respiration and from weeping wounds and due to incontinence. Radio-isotope dilution techniques were used in selected cases to measure the body content of sodium, potassium, and water. Balance techniques during

repletion provided a valuable check upon the accuracy of estimates of deficits.

Once all this knowledge had been assembled it was no longer necessary as a matter of routine to use weigh beds, isotope dilution, or even to measure the electrolyte composition of all the fluid coming out of the body. An accurate fluid intake and output chart with empirical knowledge of the probable composition of fluids coming from different sources and circumstances would permit an appropriate choice of the fluids to be infused. It would be an exaggeration to claim that all fluid balance problems can now be handled by junior hospital staff, but most of them are, using simple rules, a balance chart, and a measure of the central venous pressure. The latter measurement made through the same catheter used for the infusion, with a simple water manometer, avoids the danger of overloading the circulation with excessive fluid.

A dramatic illustration of the effectiveness of such methods comes from the treatment of cholera (26). Untreated, 40–80 per cent of patients may die, some within 10 hours of the onset of symptoms. The fluid loss by diarrhoea is usually 300–500 ml per hour, but may reach 1·5 litres an hour. Rapid intravenous replacement will reduce the mortality to 1 per cent in the best conditions and 5 per cent in the field. As the diarrhoea lasts 3–5 days an average patient may require 30–50 litres of intravenous fluid. This is beyond the means of a very poor country. Oral replacement of an electrolyte solution leads to an increase in stool volume equal to the oral intake, so it is no help. However, a chance observation by Phillips in 1959 showed that if glucose were added to the oral electrolyte solution, the patient would go into a positive fluid balance. This observation was confirmed and extended by Hirschhorn (1968) who devised a mixture containing glucose and glycine as well as electrolytes that allowed a patient to be managed by oral therapy once the initial intravenous repletion had been accomplished.

OXYGEN THERAPY

Without an adequate supply of oxygen patients die. The importance of oxygen for the support of life was recognized soon after

its discovery by Lavoisier in 1790. The work of physiologists such as Haldane, Peters, and Barcroft defined the main characteristics of oxygen transport by the blood including the all-important oxy-haemoglobin dissociation curve. It was obvious to clinicians that cyanosed patients were short of oxygen and various devices were invented to improve oxygen delivery such as the oxygen tent and the incubator. The oxygen tent was widely used in clinical medicine, but improved knowledge of the physiological problem in chronic respiratory failure led to its abandonment and replacement by oxygen masks that delivered air enriched with small amounts of additional oxygen. The design of the Venturi mask was a result of a complex interaction of clinical needs, research on control of breathing and improvements in instruments that made possible rapid analysis of gas and blood samples for oxygen and carbon dioxide.

Up to 1952 the clinical response to a patient with hypoxia was to give oxygen at a high concentration by a face mask. If they were severely cyanosed they were placed in an oxygen tent. The immediate improvement was often gratifying but many patients with chronic respiratory failure deteriorated and eventually died despite the high concentration of oxygen in their inspired air. Westlake showed that when patients with chronic respiratory failure were placed in oxygen their carbon dioxide pressure in the arterial blood (p_aCO_2) shot up, sometimes to levels that had not been thought compatible with life. Donald and Campbell who had worked at different times with Riley at Bellevue Hospital in New York and Johns Hopkins in Baltimore brought back the bubble method of gas analysis to the UK and applied some of the concepts of gas exchange developed theoretically by Otis and Fenn. The ability to measure arterial oxygen and carbon dioxide pressure combined with improved knowledge of the physiology of the lung, suggested that it ought to be possible to increase the oxygen supply somewhat without causing the onset of CO_2 narcosis. In a normal person the depth and frequency of breathing is regulated chiefly by the p_aCO_2. In patients with slowly progressive chronic lung disease this mechanism gradually fails. The p_aCO_2 may rise to 50 per cent or more above the normal value and the drive to breathe comes mainly from lack of oxygen. If an

excess is provided the immediate result is an improvement of oxygenation. The drive to breathe is less, so respiratory gas exchange decreases. Elimination of CO_2 decreases and the p_aCO_2 begins to rise. Carbon dioxide narcosis saps the will to cough and breathe and the patient becomes locked in a vicious descending spiral. The result is coma, shallow breathing, retained pus and secretions in the bronchi and recurrence of hypoxia despite the high concentration of oxygen in the inspired air. Early attempts to improve breathing by use of stimulants of breathing were unsuccessful. Giving oxygen and keeping a close watch on the p_aCO_2 was better but the bubble method of measuring the gases was very time-consuming and the delivery systems for oxygen : air mixtures were unreliable (27). Nunn suggested the use of the Venturi principle to produce a stable mixture of air and oxygen. The great advantage of the Venturi mask was its reliability, simplicity, and insensitivity to gas flow rates. It would produce a constant admixture of gases over a tenfold range of flow rates, a very important matter for a device to be used on general wards. The final development of the Venturi mask by Campbell was greatly assisted by the availability of a respiratory mass spectrometer used as a fast gas analyser (28).

The combination of the Venturi mask, simple rules about patient management and measurements of arterial blood gases with oxygen and carbon dioxide electrodes has revolutionized the management of chronic respiratory failure. More complex methods are rarely necessary unless the patient has been mishandled by administration of excessive amounts of oxygen beforehand.

LESSONS

The most important lesson which I draw from these varied examples lies in the diversity of scientific and technical developments that made each one possible. They emphasize the interdependence of different branches of science. Laboratory science, with its ability to take systems to pieces, has a great advantage in understanding events at the molecular or cellular level. Clinical science comes into its own in the study of integrative mechanisms and the biology of man, the target species of medical research.

Both need support and both are in some danger. The cry for relevance to man is beginning to undermine the position of pre-clinical science departments in undergraduate medical schools. These departments form a large part of the national resource in the basic biological sciences. The work of clinical scientists is being distracted by current policies in the NHS and universities and by the requirements of higher medical training. It would be ironic if the search for relevance in medical education and equality in medical care ended up by damaging the prospects for future developments in both of them.

Biological systems are very complex and varied compared with most other fields of scientific inquiry. Predictions are difficult and targeted research scarcely feasible. Almost the only biomedical research that comes near to a 90 per cent chance of 'success' is minor modifications in the structure of known active drugs. Apart from the occasional surprise (for example, the loop diuretic, frusemide), this type of research only adds further unwanted structures to the lengthening list of benzodiazepines, beta-blocking drugs, etc. As biological knowledge expands limited targeting is possible, for example, a decision to seek a reversible inhibitor of a particular enzyme. Whether such a project will succeed in the biochemical/pharmacological sense is uncertain and in terms of finding an eventual therapeutic outlet, much more so.

Several strategies are available that may increase the chances of success in therapeutic research. It is useful to bring as many as possible of the relevant disciplines together in one institution and to facilitate interdisciplinary contacts. This requires an above average level of funding and a flexible organization. It has not proved easy to construct interdisciplinary teams in British universities, largely because of the small size of academic departments. The MRC have helped by founding research groups but these are more difficult to establish now because of the near impossibility of giving guarantees about take-over by the university. MRC units have an advantage in this respect although their relative isolation can be a problem.

The weakness of the present system may not be so obvious as I have deliberately not emphasized them in the same way as I have the flow lines of scientific discovery. An epidemiologist, a health

economist or a sociologist would not be slow to point out some unanswered questions. What is the long-term efficacy, safety and cost of these procedures? Allopurinol reduces serum uric acid and can disperse tophi. What happens to the attack rate of gout in the long-term especially when the drug is used as a prophylactic in patients with a high serum urate who have never had an acute attack of gout? What is the effect of cimetidine upon the long, as opposed to short-term, outlook for ulcer patients? Will it replace surgery or merely stave it off for a year or two? The Venturi mask benefits patients with chronic lung disease who lack oxygen. How much difference does any treatment make to the life expectancy and comfort of these patients once they have reached the stage of requiring hospital admission?

Answers to these questions are not a simple matter. Outcome must be measured using a number of disparate indices. Life expectancy, non-fatal complications, admissions to hospital, symptoms of the disease and the treatment, psychological changes, social disturbance of the patient and his family, loss of time from work, general well being, direct and indirect costs of treatment, etc. If two forms of treatment yield different admixtures of these factors it is difficult to compare them other than by assigning money values to each one, a process that most doctors find very disturbing and unsatisfactory.

Within these limitations, targeted research projects to evaluate the effectiveness, safety, and cost of treatment are perfectly feasible. The problem is that they do not often get done.

4

Technology. Master or slave?

Technology in medicine has received such general condemnation from commentators like Illich (1) and Horrobin (29), who agree about little else, that I think it is necessary to say a word in its defence. Non-scientists often assume that ideas are the currency of science and that techniques and technology are for lesser mortals at the applied end of the business. This may be true for a theoretical physicist like Einstein but it is not true of the applied sciences such as medicine which are heavily dependent upon technological methods and becoming more so. It is impossible to apply the correct treatment if the nature and extent of the disease is unknown. A very important impediment to research upon coronary artery disease has been the difficulty of assessing the extent of the lesions and their response to treatment. If there were a method with a little higher definition than coronary arteriography and which could safely be repeated at short intervals the possibility of finding a treatment for coronary atheroma would be enormously enhanced.

Looking inside the human body without harming it is the theme of the methods that I have chosen to review. Each embodies the use of high technology and they are all expensive, some are very expensive indeed. They combine greater certainty with less discomfort and risk. Why then are they the subject of so much criticism?

Three main criticisms are made of new diagnostic methods that rely upon sophisticated machines. The first is that their owners are seduced by them. Instead of being a jolly good clinician with a stethoscope, tendon hammer, and torch, there is the doctor as a second-rate technician half hypnotized by a row of brushed aluminium knobs and flashes of light-emitting diodes. There is no doubt that the designers of these machines know how to make

them look good, and morale lifts a little the day a new toy arrives at the laboratory. But I prefer to think the most seductive thing about them is that they are useful and a hopeful trend is that some of the new machines I shall describe yield valuable information with less discomfort and risk than the methods which they have supplanted. Would that everyone who accepts seduction had such good reason.

The second criticism concerns the inhumanity and frightening aspect of machines. I wonder how valid this criticism is. When half the population have seen *Star Wars*, I doubt whether contact with medical instruments that are often no more complex than a combination of a television set and a stereo-amplifier frightens patients who have been given a proper explanation and introduction to them.

The third criticism is the most forceful. It is that new technology is extremely expensive, poorly validated, and used to a greatly excessive extent. It is a point to which I must return, but meanwhile let us consider some of the methods that most often come under criticism.

FLEXIBLE ENDOSCOPY

The ability to visualize and in many cases biopsy an area of diseased tissue is a crucial component of diagnosis. The difference in prognosis between cancer of the skin and that of the lung, stomach, and colon must depend to a large extent upon the readiness with which it can be diagnosed by direct examination. Unfortunately many deep organs are relatively inaccessible to direct visualization by anyone save the surgeon, and an exploratory laparotomy cannot be undertaken lightly. Physicians and surgeons had already developed the techniques of using rigid instruments to examine the larger bronchi, the bladder, and the rectum and colon, but the invention of flexible fibre-optic endoscopes has revolutionized the study of the gastro-intestinal tract (30). These remarkable instruments about 1 metre long and 10–13 mm wide can be manipulated around the loops and corners of the gastro-intestinal tract, so that it is possible for one instrument coming from above through the mouth to meet one coming from below

through the anus. The distal tip, 5–6 cm long can be turned through 180° in any direction. Their use has greatly improved the precision of the diagnoses of carcinoma of stomach and the source of upper gastro-intestinal bleeding. They have made possible the cannulation of the ampulla of Vater and improved diagnosis of disorders of the biliary tree and the pancreas. They have also greatly facilitated the correct diagnosis of lesions of the colon, especially neoplasms. Flexible forceps, 2 mm in diameter, can be passed through to take biopsies and even to remove gall-stones.

In many cases their use should not only have improved diagnosis but saved cost. The competing techniques are almost always radiological, and the accuracy of the endoscopic methods appears to be greater. Each requires skilled operators, but the equipment used in radiology is considerably more expensive than even the most expensive endoscopes. Unfortunately some medical staff prefer to use a belt and braces approach and to carry out both X-rays and endoscopy. Increasing confidence in the endoscopic technique and definition of its field of usefulness seems likely to end some of this expensive duplication. There may also be a problem in limiting its use to proven indicators, because endoscopy is easier than a radiological procedure to arrange and is not governed by the same limitations of equipment.

ULTRASONIC ECHO TECHNIQUES

Cardiologists above all other specialists have developed methods of invading the body with catheters to diagnose abnormalities of the heart and blood vessels. Many of these techniques are uncomfortable and they are not free of risk. The development of ultrasonic methods hold out the hope that many radiological and catheterization studies may prove to be unnecessary. The principle of the ultrasonic method is exactly the same as that of the echo-sounder or 'fish finder'. An ultrasonic pulse from a piezo-electric crystal is sent into the tissues about 1,000 times a second, and the reflections from surfaces where there is a change in density are detected and displayed. The simplest device will use only a single detector and sensor, but much more complex instruments have been developed with the arrays of detectors and sensors which

enable an image to be built up which can be viewed like a slice across the body. When a train of rapidly repeated pulses is sent with appropriate instrumentation it is possible to measure the velocity and character of the movement of a moving structure. Thus these techniques can be used to detect and quantitate a pericardial infusion, to measure the size of the cavity of the left-ventricle, the movements of its wall and the cusps of the mitral valve. Ultrasound has proved highly effective in detecting and evaluating disorders of the mitral valve cusps and of the heart muscle itself (31). Besides its use in cardiology, ultrasound is being used in the abdomen to detect secondary tumours in the liver and cysts in the kidney, in the brain, to study the foetus in the uterus, and so on. Ultrasound is a non-invasive, completely painless, safe, and un-frightening technique which is to some extent superseding other methods which cause pain, discomfort, and risk.

RADIO-ISOTOPE SCANNING

If one type of tissue can be persuaded to concentrate a radio-active isotope more than other tissues there is the possibility that the activity of this concentrating process can be measured and be detected by appropriate equipment and displayed as an image. Early scanners relied upon moving a single detector in a single plane across the body. This technique is still used by an array of detectors to display more information, or a single large crystal can be used in a pinhole camera designed to display the distribution of a gamma ray emitting isotope in the body. These techniques can be combined with use of extremely short-lived radio-active isotopes, whose half-life is measured in seconds or minutes to display the blood flow and activity of organs in a two-dimensional picture while delivering acceptably low doses of radio-isotopes. Thus oxygen-15 has been used to display the distribution of blood flow in the brain and krypton-81m to measure the distribution of air and blood in the lung. A number of bone-seeking isotopes with longer half-lives are used to detect metastases of cancers in bone. The latter technique is of particular importance when a decision is being made about the most appropriate method of treatment of cancer. Intensive local radiotherapy

would not be worth while if there were deposits of tumour remote from the site to be treated.

COMPUTERIZED AXIAL TOMOGRAPHY

Computerized axial tomography (CAT) is at once the wonder child of diagnostic technology and the bogey man of health economists. A highly original combination of the well-known X-ray technique of tomography, which displays an image of a body slice, with a high-speed digital computer allows an image of a body slide to be displayed in varying levels of density contrast. CAT scanning has been most widely used to detect tumours and haemorrhages in the brain. There is no doubt in the mind of anyone who has seen the pictures that it is a most valuable addition to neurological diagnosis. The alternative techniques of diagnosis are by angiography or air encephalography and these are very uncomfortable and not free of risk. A whole body version of the scanner has been devised. It is already adding to the precision of diagnosis of conditions such as tumours of the adrenal and pancreas, and asbestosis of the pleura (32). The eventual capabilities of the technique have still to be defined and further improvements in the technology are taking place.

The CAT scanner has improved the precision of diagnosis and diminished risk and discomfort. With these sterling advantages why has it become the most widely quoted example of the problems of advanced technology applied to health service work? The main reason is its high cost. Different models and specifications vary from about £300,000 to £750,000. Few British hospitals have been able to afford these prices and the spread of instruments in Britain has been slow. In the United States the machine is a revenue earner and very large numbers of instruments have been acquired. A large hospital may have more than one, even smallish hospitals may have one. Having made such an expensive investment the pressure to use it must be strong. Neurological clinics are swamped with patients complaining of persistent headaches. Most of them do not have a serious cause such as a brain haemorrage or brain tumour. In Britain the lack of availability of scanners has meant that neurologists have had to be highly selective, perhaps in some cases too selective, about the kind

of patients they refer for CAT scans. In the United States many scans must have been done without there having been an adequate indication or a real prospect of a positive finding.

BAD TECHNOLOGY, BAD DOCTORS, OR A BADLY RUN HEALTH SERVICE?

It would be just conceivable that a very expensive instrument could be foisted on one or two major hospitals, that ultimately proved to be completely useless. I can think of one or two examples that involved incompletely developed prototypes of complete machines. But the word spreads quickly and no-one else will buy until the manufacturer has rectified the faults. None of the techniques I have described suffer from that problem. They work and are reasonably reliable. The technology is good. When properly used they provide information of such obvious value in some patients that there is little room for doubt about its usefulness. But they are costly and the cost is highly visible. Salaries which are often even more expensive are more easily forgotten. Indeed those who complain about the cost of the machines often forget the running costs which can be greater than the initial capital cost. So the problem is not so much with the technique itself but how it is used and this concerns effectiveness and cost (33). Many of the problems that complicate and occasionally confound the evaluation of drugs and surgery do not apply to the investigation of new technology. The result of measurement depends only to a very small extent upon the biology of the individual, so that the major source of variability in judging therapeutic responses has been removed. Thus it ought to be possible to arrange clinical trials of major instruments like the CAT scanner and ultrasonic echo machines and reach a fairly high degree of agreement about the type and number of patients who would benefit from the availability of the method, and its cost-effectiveness in comparison with alternatives. Based on this data the number of machines required and their geographical distribution could be planned. It would be worth doing this even if the plan could not be implemented at once. An opportunity for doing this was lost when the CAT scanner, a British invention, was introduced.

I foresee two major barriers to such a rigorous evaluation. The first lies with the users. Natural curiosity and lack of complete confidence in a new method often means it will be used for a time alongside the old one. Unfortunately this state of affairs may become permanent when a more critical appraisal would have led to one or the other being abandoned. Currently many patients are having both endoscopic examinations and barium X-ray studies for gastro-intestinal tract lesions. Both CAT scans and angiography are used even when one method has already clearly identified the lesion. Some way of checking the perpetual addition of techniques must be found. The second problem is that no organization exists whose responsibility it is to carry out vigorous comparative trials of diagnostic methods. Some performance testing of instruments is carried out by the DHSS and the results circulated in newsletters but this is not a substitute for comparative studies of diagnostic methods. The logic of diagnosis is more akin to the recognition of a picture on an incomplete jigsaw than the strict algorithm of a computer program. There may be several ways of gaining the same degree of certainty and the additional precision from expensive further tests may be quite small. There is a problem of conceptualizing the process of diagnosis and separating out the components which are necessary and those which are due to curiosity or the desire for additional reassurance. What level of certainty is appropriate for different degrees of disease severity? Evidently much depends upon the change in patient management that might result from the investigation. If the probability is that there will be no change, it is highly questionable whether the test should be done at all. This is the kind of research which well-motivated practitioners ought to be able to undertake provided that they are given appropriate training, encouragement, and advice concerning experimental design and statistical analysis.

The answer to the question posed by the title of this section seems to be that the technology itself is not to blame; the doctors, as usual, are being rather uncritical, but the main problem lies with the provision of comparative information upon which they can make a better informed judgement. With one or two of the major techniques, it seems a suitable topic for research.

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Future hopes and problems

The present, largely unplanned method of making scientific discoveries and applying them to medicine has worked well. I believe that there are good grounds for anticipating future achievements at least comparable to those of the last thirty years. The environment in which they will be made and exploited is more complex and in some respects less flexible than in the past. The responsible organizations, the Medical Research Council, the universities, and the National Health Service will have to show a great deal of ingenuity and flexibility themselves to surmount and avoid the obstacles to progress. The application of research discoveries to health care is less satisfactory and the organization of research in this field needs improving if the full benefit of discoveries in science and technology is to be attained.

FUTURE HOPES FROM MEDICAL RESEARCH

The stream of major discoveries in biology has been a comparatively recent development. It has run at its present strength for only thirty or forty years. It shows no sign of slackening Important new discoveries in the basic sciences continue apace, many with promising applications to human disease.

The detailed knowledge of the coagulation process that has sprung from research on the chain reaction of serine protease enzymes that eventually produce a clot of fibrin is of particular interest. These enzymes appear to be hung on the surface of the platelet by a recently discovered diacarboxylic acid. At a stroke this achieves a high local concentration to enable the chain reaction to go faster and also to deliver the coagulation proteins to the site of bleeding by riding piggy-back on the platelets. A great deal has been learnt very recently about how the platelets

stick to a site of bleeding or other vessel wall damage. Platelets adhering to the damaged wall release a fatty acid-like material named thromoxane A2 and this is a very powerful promoter of further platelet aggregation. There is also an antagonist system which relies upon a closely related compound, prostacyclin, to prevent aggregation. Prostacyclin is released from blood vessel walls and from the lung. This delicately balanced mechanism is disturbed when coagulation takes place. Knowledge of it seems certain to mean important developments in the treatment and prevention of intravascular thrombosis.

The recent discovery that there is a natural receptor in the brain concerned with the regulation of pain perception is one of great fascination. Morphine binds to this receptor whose natural antagonists are a group of peptides called encephalins derived from a group of larger molecules, the endorphins. Will this discovery facilitate the long-standing aim of separating the addictive and analgesic properties of the opiates?

The science of immunology has been expanding fastest of all. Individual genetic differences in the cell surface antigens of the A, B, C, and D series of the HLA group play an important part in determining individual susceptibility to disease. These antigens seem to be concerned particularly with resistance to virus infections, but by no means all the diseases that have shown a statistical association with the HLA sub-types are thought to be of viral origin. Two in this category are ankylosing spondylitis, a chronic inflammatory disease of the spine and psoriasis, a common inherited skin disorder causing raised red flaky patches all over the body surface. While the possibility of genetic engineering in man still seems remote, although no longer inconceivable, advances in the laboratory have opened the door to large-scale production of proteins such as immunoglobulins. One of these techniques, devised by Millstein in the MRC Laboratory of Molecular Biology, involves the fusion of the genetic material of two cells. If one of these is a mouse myeloma cell, whose normal function is to produce large quantities of a single protein, the fused cell line can be an efficient producer of a desired protein from the other cell. The tumour is re-implanted in a mouse and can be propagated indefinitely. Another trick of genetic engineering is to manipulate

the rings of DNA called plasmids which are found in bacteria. The ring can be cut open with an enzyme and have an alien length of DNA stitched into it by another enzyme. The ring is closed by a third enzyme and then re-implanted in the bacterium. If the alien DNA code is for a protein such as insulin, the bacteria will now produce it. The problems of producing large amounts of protein have yet to be solved but the technique has enormous promise. It might, for example, solve the world shortage of insulin to treat diabetes.

These developments, and many more like them, provide a powerful argument for continuing a major investment in the biological sciences with the aim of improving human health. But to my mind there is an even more powerful argument from the many common diseases for which we can do so little. This is true of most deep cancers, most atheromatous disease of arteries and for a great many afflicted with mental illnesses such as schizophrenia and dementia. Some of these conditions may be preventable, others are probably not. Even those that are preventable may prove to be more difficult to prevent than to treat. Each one of those I have mentioned is probably amenable to a biochemical attack. A major breakthrough in one of them might change the rules entirely as did the discovery of anti-tuberculous chemotherapy. I cannot say where in the spectrum of the sciences such a discovery may come, but I believe that it is possible.

Unfortunately, many people, including some of the most senior in the medical research hierarchy, are pessimistic about the chances of future advance. It seems to be a characteristic of senior and very distinguished investigators as they look back on their own great achievements, to feel that it has all been done and there is nothing left to look forward to. Men as distinguished in their times as Billroth, Burnett, and Rosenheim have made statements that could be read in this way towards the end of their careers. Such a pessimistic view has never been justified in the past, and I am quite certain that it is not at present.

A second type of pessimism is to devalue the discoveries that been made rather than to be exhilarated by them. The pessimists are sadly wrong. A decade that has seen the introduction of l-dopa for Parkinson's Disease, propranolol for angina and hypertension

and cimetidine for peptic ulcer can only be regarded as an era of brilliant success. It sometimes seems as though medical research workers must make a discovery equivalent to the jet engine or nuclear power station every year if they are to fulfil public expectations and keep at bay the pessimists who are so ready to say that it is all over now apart from a tidying-up operation.

PROBLEMS WITH APPLIED RESEARCH AND DEVELOPMENT

Research designed to discover new methods of treatment is a continuum from the innovator to eventual application in the community. Without a flow of new ideas the whole system can only mark time. Those ideas are likely to be expressed in molecular terms if the new invention is a drug and in electro-mechanical ones if it is a diagnostic or therapeutic machine. While I anticipate further improvement in surgical methods I do not expect any radically new departures unless these are combined with use of new drugs or devices. The majority of diseases that cannot now be cured by surgical means, and this unfortunately means most malignancies, are likely to remain in that category.

The benefits of scientific advances can only be reaped if they are properly tested and developed into a form that is suitable for general use. Many factors are involved in the development and application process, by no means all of them strictly scientific. New discoveries are of little use to a community that cannot afford them and this is beginning to be the case for some very expensive procedures, such as renal dialysis, in Britain. The organization of medical services, the quality of care, and the social context make an important difference to the outcome of treatments that are highly effective in optimal conditions. Many new forms of treatment involve long-term ingestion of complex drug regimes. Failure to take the drugs as prescribed is the main cause of unsatisfactory results from such regimes. Socially deprived groups, the elderly, single people living alone, alcoholics, mentally subnormal, are those who are least likely to comply with advice and thereby fail to secure optimal benefit. Even if the medical system is good and the social framework is strong, a new treatment must be simplified and developed into a form that is easy to apply. In

the course of simplification there is likely to be a broader definition of suitable patients and narrowing of the range of dose that is used. Further research will then be needed to redefine the usefulness of the treatment in its developed form. As drug therapy moves more and more into very long-term control of chronic illness, the late outcome becomes a most important consideration. Many forms of treatment that the medical profession has accepted in good faith control a feature of the disease, such as an elevated blood sugar in diabetes, but do they affect the late outcome, and, if they do, where lies the balance of benefit to risk? In this instance evidence has accumulated that several of the drugs used to lower blood sugar bring little benefit for life expectancy and one of them, phenformin, had an appreciable risk of causing death in lactic acidosis. Trials to investigate long-term therapy are difficult to undertake and very expensive. They do not attract the best scientists and have tended to be somewhat neglected by research organizations that respond to requests rather than identify needs.

The problems posed by the needs of applied research and development are wide and the attack on them has been much less successful than the support of basic laboratory and clinical research. The organizations concerned are the same, with the important addition of industry in the shape of pharmaceutical companies and instrument-makers. There are major difficulties with facilities, personnel, and research administration which are compounded by a sense of frustration with the results of the post-Rothschild reorganization. The very complexity of the issues involved makes it difficult to discuss them without reference to the detailed administrative arrangements as they now exist and might be changed in future. So far as possible I will sketch the main issues, but at the risk of being accused of over-simplification.

THE ROLE OF INDUSTRY

In most industrialized countries the discovery of new drugs and medical instruments is not the responsibility of the health service, a research council, or the universities but of privately owned companies. Industrial research feeds on ideas which mainly originate in universities and other governmentally supported research laboratories. Private industrial companies have proved

highly effective in turning new ideas into patentable chemical structures and developing these through all stages of testing up to the point that they are licensed for sale and can be prescribed by doctors. Industrial companies have also shown their potential in developing new ideas for instruments such as the role of EMI in the development of the technique of computerized axial tomography. Thus, in two of the most important fields relevant to human health, the development phase is almost entirely in the hands of industry. Because of the scale of operation and breadth of skills required it seems likely to remain so. Both the strengths and limitations of this situation need to be understood.

The strength of the arrangement is that a single customer with a very limited range of objectives is controlling the whole programme. There is little doubt that Lord Rothschild's experience in industry of the speed and intensity with which such a programme can be advanced led him to advocate the customer–contractor principle for government sponsored R & D. In the health field it is a system which also has some significant disadvantages. A pharmaceutical or instrument company has only a limited amount of money and skilled people and will wish to re-deploy them on new projects once an existing one is established and profitable. There is little incentive to monitor the long-term performance of the drug or instrument apart from the aspects of safety and product support. In the drug field long-term monitoring of safety has not been adequate, but the likelihood of strict liability applying to drugs as well as consumer products may provide an incentive to improved performance. Long-term studies of efficacy are much less likely to be sponsored by industry except when they are sure that they have a world-beater in their hands. But the community needs to know the long-term effectiveness and efficiency of new developments so that their priority can be assessed objectively. Commercial companies survive by selling their products and promote them with great energy. It is improbable that a commercial company will undertake a long-term trial which may show that their product is no more effective (but more expensive) than a competing one. If they do such a trial at all they will choose a softer comparison which may show their compound in a better light. A company selling a new instrument will not

fund research to show that if it is properly used the market will be much smaller than their sales department secretly hope. If the issues are minor these matters can be left to the market place to decide, but, when they are major, publicly funded research organizations must take a hand, something that they have frequently failed to do. The motives are complex. There has been a strong feeling amongst senior scientists advising the MRC that they should not pay any of the development costs of industry and in any case research applied to service needs should be funded and administered from some other source.

I see a need to recognize the interdependence of academic, industrial, and health service research. Industry may provide the jam in the middle of the sandwich, in more than one sense, but public funding and impartial evaluation should be brought in to help with assessment of major new industrial developments once their sponsors have brought them to the market-place. It is a difficult field because the patent-holder may not want anyone meddling with the prospects of commercial success of his invention while the best scientists are rarely interested in grinding protocol research. The whole patch of nettles cannot be grasped at once but some of the more prominent plants might form a suitable case for investigation.

REGULATION OF DEVELOPMENT

The development of new drugs is regulated by law, procedures such as surgical operations, new methods of rehabilitation, a different pattern of community care are not. There are interesting comparisons to be made and lessons to be learnt from regulation on the one hand and *laissez-faire* on the other.

In Britain both the decision to administer a new drug to sick people and the eventual authority to market it are subject to obtaining permission from the Medicines Division of the DHSS which is advised by an expert committee, the Committee on Safety of Medicines (CSM). The first stage requires the issue of a clinical trial certificate (CTC). The CTC is only issued after review of the pharmacology and toxicology carried out in animals and a statement about the type of patient to be studied, the dose and duration of treatment and the names of the clinical

investigators. Clinical studies can then proceed and often take several years to bring to the point of a decision to market the drug. By that time many hundreds of patients will probably have been treated, some of them for over a year. A marketing submission is a massive document which contains details of all the studies that have been carried out with statistical analyses of the evidence obtained to support each therapeutic indication and claim. In the USA individual report forms on every patient studied must be included and filing a submission with the US Food and Drug Administration (FDA) may involve delivery of a lorry-load of documents.

This procedure has some obvious strengths. The quality of evidence supplied in a submission for a major market such as the United States is high and prepared in enormous detail. It has been claimed, with reason, that studies which meet the requirements of the Food and Drug Administration in the United States are carried out to a much higher standard than the usual run of academic investigations. Most of the studies will have been carried out as properly controlled randomized double-blind trials with a full statistical analysis. Regular tests for adverse effects upon blood, liver or kidney will have been made. Most of the patients will have been traced and deaths or unexplained illness investigated.

The conduct of research on a new drug conforms closely to the customer–contractor relationship, both inside and outside the sponsor company. Originally most of the work was carried out within the innovator company, but as toxicology requirements grew, much of this work was contracted out to specialist companies. Recently, and as a direct consequence of the spread of complex fixed protocols which meet FDA requirements, many of the clinical studies are also being done on a contract basis. One patient studied strictly in accord with the protocol with all the safety data and side-effect information neatly typed on the form provided is worth X thousand dollars to the department carrying out the work. One result is that first-class academic units are becoming more and more and more reluctant to do this type of work because their opportunities for intellectual input to the study are so small. Close regulation may have raised standards but at the price of inflexibility, delay, and increased costs.

Regulation of new drug development by government agencies means that a certain minimum of information about safety and pharmacological efficacy is available before the product is launched on to the market. The information is not nearly enough to decide the ultimate value of the drug, or indeed its safety, and there will be little if any comparative information with competing forms of treatment. But at least there is some information that has been subjected to impartial external scrutiny.

The close regulation of drug development contrasts with the complete lack of it in other fields. Could the same methods of regulation be applied to other fairly well-defined forms of investigation or treatment such as surgical operations and diagnostic procedures?

Many of us have spoken half jokingly of establishing a 'Committee on Safety of Surgery' to license new operations and imagined, gleefully, the occasion when a licence for a cardiac transplantation was summarily rejected. But there are grounds for doubting whether it would be practical to try such a procedure even on a voluntary basis. Would the Royal College of Surgeons care to try? A drug is a consistent product, usually from a single source that can be controlled relatively easily. Even for drugs there is always an escape clause that allows the individual clinician in the exercise of his judgement to use a drug for a purpose for which it is not licensed. Rather than getting involved in a profitless argument about clinical freedom, it seems better to try and mobilize the intelligence and goodwill of the medical profession by providing them with accurate evidence about the efficacy, safety, and cost of new procedures as well as new drugs. But whose responsibility is it to set up and operate such an organization if it is judged to be a desirable development? In any case there is by no means universal agreement that such an organization could produce results which are superior to the normal ebb and flow of clinical practice and the interplay of market forces. I have been surprised by the vehemence of argument, even amongst some senior scientists with unimpeachable research credentials, about the undesirability of attempting it.

The protagonists of the *laissez-faire* view quote the relative lack of success of the cancer programme in the United States and the

failure of the attempt to establish an effective research organization concerned with health care at the DHSS. They believe that money poured into an area that is unripe for development will be wasted and that ideas and individuals are much more important than problems and needs. A secretary of the Medical Research Council once said that no government edict was needed to persuade him that it would be a good idea to discover a cure for heart disease and cancer; the problem was to develop a researchable idea that had some prospect of success. Although I am not a supporter of the *laissez-faire* view, I have found more substance in the argument that I expected, and have been particularly interested in the answers to two problems that I bring forward as an argument for better regulation of development. These concern intensive coronary care and by-pass vein grafts in coronary disease. The first argument begins with the premise that it may be proved that there are no benefits of admission to an intensive care unit in hospital after an acute myocardial infarction.

Supposing that this finding was generally accepted, how would it alter practice? The argument runs that it would alter very little, for the following reasons. There is a general expectation that a patient with a serious risk of death should be admitted to hospital. Would this expectation alter even if the risk of death was the same in hospital and at home. Probably not it is contended. Once the patient is in hospital what do you do? If he is in shock do you withhold treatment? No, this would be unacceptable, so he will receive whatever treatment is currently under study, or in fashion for shock: dopamine, sodium nitroprusside, etc. The patient will still be at risk of death from cardiac arrhythmia. Do you wait for him to be found dead in bed or do you, as a precaution, wire him up to a monitor oscilloscope? Probably the latter. If he suffers the onset of ventricular fibrillation or asystole do you leave him to die? No, you cannot do that, so perhaps he had better be nursed in an area where resuscitation services are close at hand. And in a few steps of argument one is back to something that looks very like a coronary care unit!

A different basis is used to argue for a *laissez-faire* approach to the development of by-pass coronary grafts. Would randomized controlled trials have been allowed to continue in the face of the

early mortality from angiography and surgery? It seems quite possible that they might have been stopped, although the mortality subsequently declined as those concerned became more practised. Suppose a randomized controlled trial had been carried out at that stage and had shown no benefit (as is most likely) would further work have been banned? In an authoritarian system conceivably it might. But now, say the believers, widespread use of the procedure has identified a group of patients with left main stem coronary artery disease who really benefit from surgery. We, the enthusiasts, were right all along and if we had let you force us into a randomized controlled trial too soon, the whole thing might have been condemned, incorrectly.

The advocates of the randomized controlled trial take a diametrically opposed view. They point to the enormous waste of resources that comes from widespread adoption of methods that later prove to have no worth. Screening of apparently healthy people, both clinical, pathological, and biochemical is cited as an example. Those who argue that something is worth while should be obliged to bring forward some acceptable evidence that what they say is true before the community is hustled into adopting it. Practically every hospital worthy of the name has spent money on expensive facilities for intensive care of the coronary crisis. That money would have been better spent on forms of treatment of proven worth. Even if work on coronary artery by-pass surgery would have been slowed down by the need to prove successive claims, would that have been a bad thing and was it not obvious that a stenosis at the origin of the left coronary artery was the lesion most likely to carry the highest risk and be the most amenable to surgery? Could not the same conclusion have been reached a year or two later with billions of dollars saved and tens of thousands of patients spared unsuccessful operations?

Although I incline much more to the second than to the first of these views, both in their extreme forms may be fallacious. The first exposes us to the poorly validated conclusions of optimistic enthusiasts and the second might bog us down in an enormous number of expensive, protracted and negative clinical trials, each dealing with a development that was in itself minor, but when aggregated with many others might have been worth while.

Major new developments must be tested in the crucible of the randomized controlled clinical outcome trial, but it is a matter of fine judgement to know both when it is too early in development to undertake it and when it may be too late. New ideas are not usually born full grown. To start a large-scale trial on outcome before sufficient information is available about the range of dose required or the type of patient most suitable for inclusion, may produce a misleading negative result. Unfortunately, if the initiation of a trial is delayed too long the new method may have been assimilated into clinical practice and a randomized controlled study may become impracticable.

Powerful tools though they are, randomized controlled outcome trials will not solve all our problems. In theory, they can be used in any situation where two or more alternative courses of action can be defined. In practice, the time, cost, and difficulty make it necessary to confine outcome trials to major therapeutic issues.

I must make it clear that I am not arguing against the general use of the techniques of randomization and control in medical research. They are part of the fabric of experimental science. My comments refer specifically to studies concerning the outcome of medical procedures and treatments.

COST AND BENEFIT FOR THE COMMUNITY

New drugs, new technology, and new methods of care usually turn out to be more expensive than the methods they have superseded. There are only a few examples, such as the conquest of tuberculosis, where massive savings accrued from a new form of treatment. In an expanding budget new methods can be welcomed and take their place alongside existing ones. When the budget is static there is a great danger that innovation will be squeezed out because there is no room for manoeuvre within the existing resources. If the momentum of innovation is to be obtained there will have to be some re-allocation of resources as well as a search for new ones. Re-allocation means closing down down or restricting existing activities to make resources available for more cost-effective new ones. Will it prove possible to re-allocate the personnel, operating theatres, and revenue costs now

devoted to the surgical treatment of peptic ulcer if the histamine-2 receptor antagonists prove as effective on the long-term as they have on the short? It will certainly be very difficult and I doubt if it could even be contemplated without good clinical trial evidence about outcome and quality of life in patients treated with long-term cimetidine versus patients subjected to vagotomy and pyloroplasty. Are such studies being planned?

One of the main arguments for comparative testing of methods of treatment and care lies in their relevance to resource allocation. Unless we do this there is a danger of ossification of existing practices which are consuming all available resources. Good comparative trials should also provide the ammunition for arguments to maintain and even increase the allocation of resources to therapeutic services. If it is impossible to prove benefits that justify costs, those resources will not be forthcoming. The benefits themselves must be measured more accurately than in the past. They will include mortality, morbidity, and to an increasing extent, comfort. The quality of life is important. When much consumer expenditure is no longer concerned with survival but with comfort in the home, the garden, and the motor-car it would be foolish to exempt medicine. Many diseases that never kill are very uncomfortable and relief of discomfort is an important medical benefit.

These considerations lead me to contend that both the community at large and the medical scientists have a common interest in seeing better provisions made for research into the application of new methods to health care. The community needs to know whether the shining new ideas from the scientists will retain their glitter when exposed to the wind and rain of routine medical practice. The scientists want to see their ideas put to use and they may not be unless there is better evidence of their practical value in comparison with alternatives.

If the objective is admitted to be desirable, its attainment will be very difficult. There are so many problems that might be researched. Most of them are rather ill-defined and there is a lack of trained personnel. The conceptual basis of research that uses soft outcome criteria such as quality of life is still weak. The temptation to launch an attack on a very wide front is strong but the chances of success correspondingly very small. A research

organization in this field will need great skill to identify a small number of problems that are worthy of attention and ripe for solution. The difficult issues raised by the need to provide a framework for fostering applied research and development in medicine form the subject of the final sections of this chapter.

THE FRAMEWORK OF GOVERNMENT SUPPORT FOR MEDICAL RESEARCH

The aim of research support in science is to increase knowledge or in more sophisticated language to discover rational correlations and principles (Rothschild). The administrative framework is there solely to provide financial support and a favourable working environment for the scientists. There is no point in supporting second-rate science at the basic level. Rediscovering in England what is already well known in Boston, Mass., or vice versa, is simple a waste of national and world resources. Organizations dedicated to supporting basic research must, therefore, espouse an uncompromising élitist policy. It is a policy that does not always sit easily with current concepts of job security, union representation, staff consultation, and the like. One of the problems is that a first-rate research organization has only limited opportunities for utilizing workers who have passed their intellectual peak, or never fulfilled their promise. While research budgets expanded and movement was easier between research council staff, the university and the national health service this was matter of little consequence. In a steady-state budget with a young staff and more impediments to mobility there could be a serious deterioration in performance of establishments dedicated to research but isolated from organizations that can provide alternative outlets in teaching, administration and service work.

The administrative structure that best reflects the élitist outlook of basic research support is the grants committee.

A grants committee makes great efforts to secure impartial and objective assessment of the scientific merit of spontaneous applications. The committee will be made up of ten to fifteen experts whose knowledge spans the field of work allocated to it. Applications are sent to several referees whose reports are seen in

full only by the chairman and the committee member charged with introducing that item. After it has discussed the application and heard the referees' opinions the committee vote in secret. In Britain a scale of 0 to 6 is often used, zero being irredeemably bad and 6 superlative. The cut-off point will depend upon the funds available but usually lies between 3 and 4. Whether the committee itself makes the eventual award or the decision is reviewed by a Board that gives weight to policy priorities and cost-effectiveness depends upon circumstances. I have served on grants committees at the MRC, its French equivalent the INSERM, and the DHSS. With minor differences in detail all use similar methods. The system relies heavily upon the quality of refereeing and the cohesion of the committee. The experience and reputation of the research organization also makes a difference. I have noted a much greater tendency of applicants to argue, sometimes quite unreasonably, with the decisions of the grants committee to which I belong at the DHSS than I encountered at the MRC. One of the most precious assets of a grant-giving organization is a good list of referees culled of those who will not take the time or trouble to give a balanced well-argued opinion. The committee members cannot possibly understand the detail of every application. The majority, who cannot understand the minutiae, are the jury who judge the applicant, the referees, and the committee members who are expert in that field. Grants committees take on a collective personality and the span of marking is usually less wide than one would expect. When I first took the chair of the Small Grants Committee at the DHSS, which has roughly equal numbers of members from the medical and social sciences, a civil servant suggested that it was likely that the medical members would vote for all medical applications and against all sociological ones, and vice versa! This gloomy prophecy proved wrong, as I anticipated it would, and only rarely does that committee split on disciplinary lines, although its breadth of interest is exceptionally wide. It is a system based upon mutual confidence but there is always a possibility that prejudices may come to be shared as well as understanding. Regular rotation of membership helps protect against this sort of bias. Those who administer grants committees sometimes come

to have an almost mystical belief in the virtues of the marking system. I suppose that they have to, when a mark of 3·5 might mean a grant of £40,000 and one of 3·2 mean a refusal of all support. It is quite certain that such a small difference is not statistically significant. The system is one of rough justice but it is hard to think of a fairer method that would not be enormously more complicated to administer.

The greatest virtue of project grant support is that it is long enough for a research worker to show whether or not his bright idea is worth pursuing but not long enough to commit him or the grant-giving body irrevocably if it does not work out. Longer-term support is given to established workers through programme grants and establishing units.

The élitist philosophy of the MRC and similar bodies has been brilliantly successful in fostering new scientific ideas but it is not free of problems when it comes to more applied aspects of science. An observer from afar might assume that since we have a Science Research Council and a Medical Research Council that the former is for research in science and the latter for medicine. This is not so. The major support for basic research in biological science comes from the MRC and this accounts for some of its schizophrenia about applied research. The justification of applied research is its targeting upon medical problems but basic research is not supported just because it may one day provide the foundation for a targeted programme. Science is to be judged and justified as an intellectual activity as well as a practical one, and the brightest scientists are usually more interested in the former than the latter. Two of the most challenging areas of science at the present time are the physics of the universe and the biology of complex organisms. Even if the discovery of the genetic code had no practical application it would still count as one of the great achievements of scientific man, comparable with the discovery of neutron stars and black holes. Biology is in a state of ferment, bubbling over with ideas as have few sciences at any time in history. The justification for using MRC funds to support basic biological research is not solely by its practical application but that it is a worthwhile end in itself and represents one of the greatest remaining challenges to the human intellect (34).

The MRC must find the money for both basic biology and applied research within a limited budget. Not surprising perhaps, that it has occasionally been hesitant about promoting tedious but important clinical trials when it knew that it had under its wing scientists who could make discoveries that would be remembered when the names of the drugs used in the trial would have passed into oblivion. This hesitancy fostered discontent amongst scientists at the applied end and among officials in the health department, a point I shall return to in my discussion of applied research and development. Before doing so I must consider some of the problems that are arising from shortage of funds in the universities, which affect the working of the project grant system of funding research and changes in the National Health Service which are having an adverse effect upon clinical research.

The funding of research in British universities has been founded on a dual support system. One limb comes from the university, chiefly through UGC funds. The university provides the infrastructure, laboratories, computers, libraries, administration and senior academic staff. The research councils and charities top up by providing research workers, consumable materials, instruments, etc. It is a system that has worked well in the past but it is cracking apart now because of the severe squeeze on university funds. That squeeze has had two adverse consequences. It has made universities reluctant to assume any kind of take-over commitment for successful innovations that have been initiated with research council or charitable funds. In the past such developments were taken over willingly out of development funds and this had become one of the main avenues for establishing new scientific disciplines in universities. Inability of universities to give take-over commitments is bound to hinder growth of new subjects in future. A certain caution has come to the fore even with project grants, as a department that has secured a number of these may find that its core support is insufficient to bear some of the consequential expenditure which is supposed to come from university funds under the dual support system. In the United States, because of the shortage of funds for teaching, and a relative abundance for research, it has long been the practice for grants to include a realistic figure for overheads, often 50 per cent

or more, of the amounts for direct expenditure. Indeed, the situation in the USA has produced an opposite distortion where the maintenance of core facilities has become crucially dependent upon overhead payments from grants. Loss of a major grant may then not just be a setback for the investigator but for the whole institution.

Unless the funding of British universities from the UGC shows a substantial improvement, which I judge to be somewhat unlikely, research grants will have to make provision for realistic overheads. This will reduce the total sum of money available for research and exaggerate the differences in staffing and funding of institutions successful in obtaining grants and those that are not.

MAINTENANCE OF THE SCIENTIFIC BASE OF MEDICINE

Recruitment into scientific research was bound to taper off as funding approached a steady state from a period of exponential growth. Most research workers, including team leaders, are young. If the influx has to match the outflow, which it has with the security of tenure which is now offered, the number of vacancies over the next ten to fifteen years will be many fewer than in the past. Recruitment has also suffered from the swing against science, although fortunately biological science has been favoured by bright students even during the period of maximum aversion to the physical sciences. The situation in clinical science is even more difficult than in the basic sciences and deserves special mention.

Clinical science (35) is a delicate plant strongly established in only a few centres around the world. In Britain especially it seems to be under attack from every side. Clinical scientists are for the most part on the academic staff of university hospitals, although there are smaller numbers of MRC units. Recruitment into clinical science comes mostly from young doctors who decide to spend a period in research after completing their general professional training (and passing the MRCP or equivalent examination) about two or three years after qualification. As a medical training alone often fails to provide a strong enough grounding in science, an additional qualification is needed. This may be an intercalated BSc during the medical course or a MPhil or a PhD

obtained during research training before or after qualification in medicine. Thus, the training is a long one. As specialist medical training has become more structured (and longer—four years) it has become more difficult to fit a really worth-while research experience into it, except in a few centres with very heavy staffing in the junior grades.

Clinical scientists have consultant responsibilities in their hospitals and beyond. In recent years the majority of the professions' leaders have been drawn from the chairmen of academic departments. For example, most of the recent Presidents of the Royal College of Physicians have been Professors of Medicine. The government makes heavy calls upon medical academics as advisors, committee chairmen, and members, etc. Professor Brian Emmerson of the University of Brisbane has written of the four hats of the Professor of Medicine. His clinical colleagues expect him to be a full-time clinician; his university expects him to be a full-time teacher; the research supporting agencies expect him to be a full-time research worker; and his Dean, his hospital, and the health service expect him to be a full-time administrator.

As research sessions do not have the protected timetable of ward rounds, lectures, or committee meetings, they are the first to suffer. The reorganization of the National Health Service has led to a great proliferation of committee work which requires the presence of senior clinical academic staff. The anti-teaching hospital lobby which was predominant in the DHSS in the 1960s created its own difficulties. Decision after decision emanating from the DHSS, whether it concerns reallocation of resources, redistribution of junior hospital staff, new contracts for hospital consultants, are taken without regard to the fact that they may be damaging to teaching and research in the universities. I do not accuse the DHSS in general of any wilful desire to damage academic medicine and research. When the choice is between oversight and conspiracy the former almost always turns out to be true. Indeed, the DHSS has encouraged the universities to found Chairs in shortage subjects like geriatric medicine, general practice, and radiology, and the medical schools have done their best to help. The damage that is being done stems mainly from a lack of understanding and concern, but this does not mitigate its impact.

The best solution to the problem would be a greater recognition of the importance and the need to protect clinical research by not forcing every hospital and every specialist training post into a mould that is best adapted for an average district general hospital. It is not easy to do this because there has been a quite deliberate deflation of the power of university hospitals over their own destiny and it will take time to restore the situation even when it is recognized to be necessary. Sympathetic noises are to be heard and distant mutterings about flexibility but thus far, no action.

I believe that there is a need for some public discussion of the several responsibilities of research councils, universities, and the health service in relation to fostering medical research. The current trend which is for universities to think mainly about teaching and the NHS almost entirely about provision of services is against the long-term interest of both parties. The MRC could have played a catalytic role in initiating such a dialogue but it has been excessively preoccupied with its resentment about transferred funds under the Rothschild settlement (36) and, to some extent, the problems of no growth and a tenured staff in its own establishments. As the funds spent directly and indirectly on the support of medical research by the universities and the health service are probably of the same order as those provided by the MRC it is in everyone's interest that good value is obtained and all is not lost by zealous application of puritan egalitarianism.

ADMINISTRATIVE ARRANGEMENTS FOR APPLIED MEDICAL RESEARCH AND DEVELOPMENT

Controversy about the management of applied medical research in Britain began some years ago. The MRC had been very successful in some fields such as molecular biology but there was a persistent undercurrent of criticism from the Ministry of Health that its élitist outlook meant that applied research was neglected. The MRC took little or no action concerning the health care aspects of problems such as coronary care, cervical cancer screening etc.

A major direct involvement of the DHSS in research began in the middle 1960s largely, it is said, because of this dissatisfaction

with the MRC. In the course of time direct expenditure on research by the DHSS has built up to a substantial sum, currently about £10 million per annum. The Rothschild Report in 1971 (36) gave a further powerful impetus to this trend by transferring 25 per cent of the MRC budget to the DHSS to be spent in accordance with the customer–contractor principal. The situation in Whitehall that led to the Rothschild Report is reviewed in *Five Years After*, a report compiled by Professor T. Whitehead and a Nuffield Provincial Hospitals Trust Working Party (37).

Lord Rothschild had very little to say directly about medical research in his report, a fact that was largely overlooked in the subsequent discussion which concentrated on this aspect. Rothschild's main concern was to create an effective customer organization within the Departments of State. He proposed to do this by appointment of a Chief Scientist with an appropriate supporting organization in each department. A proportion of the relevant research council budget would then be transferred to the department to be expended on contract research specified by the customer. The examples chosen in the report all referred to government purchase of tangible objects, for example, a new torpedo and improved roads, and Rothschild cautioned against open-ended commitments of an unspecific or general sort. Almost the only comment about health was to say that interaction between DHSS and SHHD on the one hand and the MRC on the other had been inadequate and needed to be rectified. This comment was followed by the recommendation that in the first instance 25 per cent of the MRC budget should be placed under the control of the DHSS/SHHD and later this might increase to 50 per cent. Uproar followed in the columns of *The Times* but the government accepted the recommendation and a Chief Scientist was appointed at the DHSS and SHHD and 25 per cent of the MRC budget was transferred to the DHSS/SHHD vote.

Looking back it seems very doubtful if Lord Rothschild gave any detailed consideration to the special problems of medical research. If he had, he would probably have realized that the type of research he had in the forefront of his mind was largely carried out by the pharmaceutical and electronic industries looking to a world market and not to any specific needs of the British

government. As the industry was not receiving research support directly from the government there was no way that the Chief Scientist or his organization could influence the type of work to which the customer–contractor relationship most obviously applied.

The creation of the Chief Scientist with his organization (CSO) was intended to give a powerful impetus to health services research but most commentators have been critical of the modest results achieved in the first five years.

The Chief Scientist was provided with a senior advisory committee, the Chief Scientist's Research Committee (CSRC), and a research board similar to an MRC board, the Health Services Research Board (HSRB). I have, from time to time, been a member of both of them. Neither has been properly serviced or provided with any real function. The HSRB was dissolved after a brief period of inward-looking inactivity and as I write it seems conceivable that the CSRC may suffer the same fate. The CSO was very small, only three people, so that it could not even service its committees fully, let alone take any effective action. The most it could hope to do was to serve a high-level advisory function, but as we shall see, there were other methods of obtaining advice and what was needed was action.

The main responsibility for defining the DHSS's needs for research has meanwhile devolved on to Research Liaison Groups (RLGs), that are gradually being established in the policy divisions which are the functional units of the Department of Health. An RLG is usually chaired by the Under-Secretary in charge of the division and it has two or three scientific advisers, usually academics, who are nominated by the Chief Scientist. As the RLGs are in the policy divisions, they reflect the organization of the Departments into divisions dealing with individual 'client groups', for example, the elderly, the mentally ill, children, etc. There is considerable disagreement about the effectiveness of the RLGs. Even when they work well, the RLGs could never hope to be the centre-piece of an effective research organization. They are too divided, fragmented, and peripheral to provide a focus for promoting health care research at the DHSS.

The main emphasis given to DHSS research has been the

interaction of health with social policy and it has throughout been orientated towards the investigation of problems rather than the generation and testing of hypotheses or evolution of concepts. The majority of members of the CSRC and the scientific advisors are drawn from social medicine or social science either as their prime discipline or sympathy. On reflection, I believe that this emphasis was excessive and has led to some of the current difficulties. This sentence should not be read as an attack on the social sciences. They have a vital role in health services research. It is simply that I believe the opportunities for carrying out some really decisive studies were better in other directions. It is always best to capitalize on one's assets and to work from the known towards the unknown. There are tremendous problems connected with the work of social workers, physiotherapists, nurses, speech therapists, etc. Archie Cochrane singled out social work (4) itself as a suitable topic for randomized controlled trial! But if there are few trained research workers in the field, commissioning research may be quite unproductive and wasteful. One problem with the commissioning process is that an RLG or a grants committee may be able to revise the research protocol into an acceptable shape but this does necessarily reprogramme the investigator so that he will do the job properly. Protocol research is a technique that requires a proper training to carry out well.

The major strength available in Britain which should have been capitalized was in the conduct of randomized controlled trials and clinical experiments generally. This expertise was initiated by Sir Austin Bradford Hill before the Second World War. Considering how distinguished were the early records of such trials in the evaluation of the treatment of tuberculosis, rheumatic fever, etc., it is suprising how little they have been exploited to investigate the problems of the last decade. If the CSO had set its main objectives as:

1. To set up an organization to collect intelligence on new developments that affected the delivery of health care;
2. To use the applied research funds to conduct trials of the most promising new developments and most questionable old ones;

3. To train promising individuals from other professions in these techniques so that they might in turn initiate them in their areas of expertise;

the story of the last five years might have been different.

To achieve these objectives it would be essential to have a highly competent organization at the centre of health services research activity to choose the relatively small number of projects to be undertaken at any one time and to provide the necessary support staff to enable them to be carried out. The intelligence-gathering function would be a most important one as I do not believe that one should rely solely upon spontaneous suggestions from the field to define the best projects. The question is how such an organization can best be provided, given that the present combination of an array of RLGs at the periphery and a minute CSO at the centre has not done so.

A POLICY-MAKING BODY FOR HEALTH SERVICES RESEARCH

The DHSS has many sources of advice. At least four different general mechanisms exist for providing that advice, besides a multitude of specific ones for drugs (CSM), food (COMA), etc. The Central Health Services Council has its standing medical advisory committee (SMAC), and the Chief Medical Officer has a group of about seventy consultant advisers who meet regularly and who represent almost every sub-specialty of medicine. There is the Chief Scientist's Organization with its Chief Scientist's Research Committee and Scientific Advisers on RLGs and finally, when any really serious problem crops up, all these bodies are likely to be ignored and a special expert group convened. All of these bodies are advisory or consultative and very lightly serviced. A man with much experience of government once defined consultation for me. The process of consultation is to ask someone's advice and then, if you do not like it, to ignore it. I think that this fairly represents the way that the advisory machinery at the DHSS is used. It seems a pity that the CSO has seen its role as predominantly advisory because Rothschild did not. He quite deliberately preferred the title 'Chief Scientist' to 'Chief Scientific Adviser'. The implication was that

the Chief Scientist would play a major role in deciding research policy. That option was never taken and the DHSS has very little in the way of a discernible research policy, especially in terms of major useful projects which might have an important effect upon the service.

Like many others I assumed that the founding of the CSRC and the HSRB signalled that the DHSS planned to set up an organization similar to the MRC, devoted to research in the field of health policy and health care (38). Apart from the names given to the committees, nothing remotely like the MRC was established.

There are signs, at present, of a desire to strengthen the CSO by amalgamating it with the research management division. I doubt if this alone will be enough. There appears to be little likelihood of an increase in the total numbers engaged in the work and the staff are already heavily committed. Projects in the health care and social science field are more difficult to evaluate than in sciences with a stronger conceptual base. Good, impartial referees are scarce. A recent proposal to create a central, well-serviced research committee was not well received by the civil service policymakers. If the present difficulties cannot be resolved I see little alternative to establishing a policymaking body for health services research elsewhere. One way of doing this would be to revive the name of the Health Services Research Board but locate it at the MRC and not the DHSS.

The terms of reference and composition of a reconstituted HSRB would have to be rather different from that of a traditional MRC Board. It would have to exercise an intelligence-gathering function as well as responding to external requests and suggestions. Its brief would be to identify new developments in medicine that appeared to be nearing the stage of general application and to carry out appropriate field trials to measure efficacy, safety, and cost-effectiveness. Some of the members would be drawn from the social sciences and economics. It would also need a budget that was, at least in part, protected. Old habits die hard and recent experience of the MRC is not entirely reassuring about its attitude to clinical trials and research into health care. It would be a pity if the opportunity were not seized to exploit our undoubted advantage in the field of clinical trials. The availability of skilled

manpower and a body with the reputation of the MRC, combined with our medical care system, which lends itself better than almost any other, to long-term follow-up, provide a unique opportunity.

If such an arrangement is implemented, there are a number of unanswered questions. Any arrangement that divides responsibility between two bodies as different in outlook and organization as the MRC and the DHSS is bound to have some rough edges along the interface.

A slimmer research management would still be required at the DHSS to service the RLGs. The RLGs would provide a suitable method for supporting data collecting and observation projects for which there is a continuing need at the DHSS. A decision about their future could be made the subject of a separate review in five to seven years time, when it will be easier to evaluate their success or failure. The Office of the Chief Scientist could be continued as the head of the rump of research management and interface with the MRC, or it could be abolished. If it is continued, there might be an advantage in giving the CSO the prime responsibility for research and intervention in disease prevention, while leaving therapeutic science to the MRC. This might give a much-needed boost to preventive measures, many of which require administrative action, often by departments other than health. Competition between MRC research workers trying to cure disease and the DHSS ones trying to prevent it, might be no bad thing.

The DHSS could retain a major influence over the long-range policy of the reconstituted HSRB by providing its income through transferred funds *à la* Rothschild. The principle of transferred funds should be abandoned for all other MRC activities. It is already little more than a time-wasting sham.

6

Conclusion

It is a paradox that serious criticism of scientific medicine has arisen when its achievements are at a peak and show no signs of a decline. The reasons are complex, in part due to changing circumstances and in part to the realization that some of the earlier uncritical acclaim was unjustified. The first major achievement of drug therapy, the conquest of most bacterial infections, was so decisive and important that what followed was bound to be something of an anti-climax (40). Once the invading bacteria has been destroyed, the patient was restored to health, often none the worse for an illness which, at its height, had brought him or her to the brink of death. Most infections are cured by short-term administration of antibiotics, thus avoiding the problems of long-term drug therapy. Bacterial cells are sufficiently different from mammalian ones for drugs to have a very high degree of selectivity in their killing power. Despite many fundamental discoveries in pharmacology and therapeutics nothing quite so decisive has ever happened since. New wonder drugs and miracle cures continue to be discovered but few of them completely and permanently eliminate the disease which they are designed to treat. They often necessitate very prolonged treatment with drugs which brings attendant problems of compliance, side-effects, and fear of serious toxicity such as occurred with thalidomide and practolol.

The sense of immense confidence in the eventual conquest of disease that came from discoveries such as penicillin and streptomycin was not confined to the medical scientists. It found strong expression in the views of politicians and the public. This was the age of Beveridge and Bevan as well as Fleming and Waksman.

Unreasonable expectations were fed by uncritical claims and a reaction was bound to come. It has come from the public in the shape of writers like Illich and from the professionals such as McKeown and Cochrane. Physicians and surgeons who had long

been happy to accept the credit for 'cures' that were due more to the placebo effect and regression upon the mean than to specific measures, were faced with the charge that their efforts had little positive effect and might even be counterproductive. It was a necessary corrective but, as so often happens in debate, the arguments against the claims of the scientists were as overstated in one direction as some of the original excessive optimism had been in the other.

Considerable progress has been made in remedying the deficiencies in applied research and development that made possible the poorly validated and misleading therapeutic claims of the past. The pioneers of this work have been medical statisticians like Sir Austin Bradford Hill and epidemiologists like Professor Archie Cochrane. Unfortunately efficacy has ceased to be the sole criterion of evaluation. The new challenge is cost.

The cost of medical care is now a serious issue for publicly funded health services as it has long been for individuals. The proportion of the national wealth devoted to health services varies somewhat in developed countries, but in all the feeling is strong that it cannot be increased greatly from its present level. A ceiling on expenditure decided centrally raises many issues, some of which are only just beginning to be faced. The dream of a comprehensive medical service providing for all patients without a barrier of cost, is fading. It seems to be a matter of policy that some procedures, such as chronic haemodialysis for terminal renal failure, are too expensive to be provided for all who might benefit from them. Increasing numbers of very elderly patients with high dependency on health and social services are making a powerful new claim upon resources; one that is destined to increase until the population age structure reaches a steady-state. Stringent testing requirements for new drugs and instruments combined with the sheer complexity of the problems has meant high prices when these innovations eventually reach the market place. Small wonder that an age of optimism has been replaced by an age of doubt.

As demands for medical services press against budgetary limits so the demand for better planning of resource allocations has increased (42, 43, 44). Demands for custodial and supportive

services can be predicted fairly precisely from a knowledge of population size and age structure but the same is not true for scientific discoveries. To a health services planner a successful innovation such as cimetidine or the CAT scanner can seem as much a burden as a boon. Where is the money to come from to pay for it? Which existing services should be curtailed? How much better it would be if the scientists could be persuaded to plan their innovations in accordance with current priorities. Unfortunately for the planners the element of surprise in scientific discovery is still so large that it is impossible to make predictions far enough ahead to be of much use to them. The danger is that no resources will be set aside for innovations.

I am confident that useful and exciting scientific discoveries applicable to medicine will continue for the foreseeable future. These discoveries will arise mainly from the complex interactions between old knowledge and new ideas and techniques that have been so fertile in the past. Predictable certainty will only come when the sciences of molecular biology and integrative mechanisms have reached the stage of a complete description of living things. This may be an attainable goal but it is one of mind-boggling complexity. One has only to reflect how little we know about such important processes as the regulation of cell growth and differentiation or the neurochemical and anatomical basis of memory to realize that we are but on the threshold of the palace of universal biological knowledge. There are limitations to what it will be possible to achieve in preventing and treating disease but we can only dimly perceive what these may be. Cells that have 'died' to the extent of losing all function and the anatomical integrity of the membranes of their organelles are unlikely to be revived. The gradual decline in function of cells with age is unlikely to be reversed but it might be slowed. Apart from these fundamental limitations there is an immense field of manoeuvre for medical science and the future prospects look excellent. It is reasonable to anticipate much better methods of dealing with cancer and heart disease but the time scale is unpredictable. It might be ten or a hundred years, no-one can say. The only certainty is that should we fail to continue support for medical research, in all its aspects, they will not happen.

Scientific discoveries cannot be planned but once they have been made it helps to have efficient arrangements for their development and testing. Such an organization requires an intelligence gathering system which can anticipate general application of new ideas by two to five years and facilitate appropriate testing of important discoveries. The need for such an organization is powerfully reinforced by the limitation of resources. In future new ideas will have to grow at the expense of older ones and that will demand a high standard of proof that the new is better than the old. Attempts to make better arrangements for administering government funds for applied medical research and development in Britain have not been a success and need to be reviewed.

Argument over allocation of resources for research and service needs between curative methods, caring services, and preventive measures seems destined to become a permanent feature of the medical scene. If rational choices are to be made, both the cost and the effectiveness of therapeutic and preventive measures will have to be tested in randomized controlled clinical trials. The greatest successes of both approaches have been against infectious diseases (antibiotics and immunization). The task of conquering degenerative diseases and cancer will be much more difficult. Prevention or treatment of these conditions may require sustained intervention in people's lives with drugs or behavioural methods. Up to now it has proved easier to persuade people to take therapeutic drugs than to give up excesses of food or social drugs. The distinction between treatment and prevention is becoming blurred as drug therapy is used as a means of primary or secondary prevention. The treatment of symptomless high blood pressure can be looked upon as an exercise in the prevention of stroke. Further refinement of methods of predicting the risk of disease based upon detailed knowledge of genetic susceptibility and environmental exposure may allow more accurate targeting of attempts at primary prevention. With very serious problems it is essential to pursue both therapeutic and preventive methods. Even if preventive methods become more effective there will be a large number of sufferers requiring treatment for years to come based upon past exposure.

Curing and caring are often portrayed as alternatives. This is a mischievous argument. Much of therapeutic medicine is concerned with comfort and well-being (41). Apart from the treatment of infections and a small number of surgical operations, medicine has few complete cures to offer. I look upon cure and care as overlapping wedges. Even at the extreme of cure, let us say in an intensive care unit after a complete repair of a congenital heart defect, the patient requires skilful nursing and help with excretory functions. At the other extreme, in a terminal care home for cancer patients, drugs have an important part to play although nursing care and human sympathy have the larger part. To be sure the relative contribution of the curing and caring services changes as age advances. It seems fair to continue to give some priority to those with their lives before them, but how much priority? At what stage of disability is it kinder to withdraw efforts to sustain life or perhaps even to hasten death with opiates or hypnotics? To many people even to pose such a question revolts by its apparent heartlessness but the problem is real and deserves informed discussion. Whatever policy is adopted, more resources will have to be diverted to providing a minimum acceptable standard of care for elderly citizens who are no longer able to lead independent lives by reason of physical or mental deterioration (45, 46).

The squeeze upon resources will have important consequences for the organization and administration of both basic and clinical research. There will be no room for the second rate because it cannot be afforded. The pursuit of excellence is the only possible course. Specialized work may have to be concentrated in fewer major centres. This may have consequences for patient treatment and health service planning. The continuum of research between basic discovery and application needs emphasizing. Those at the applied end are well aware that their efforts are of little value if no new developments are coming forward to be investigated. The hard scientists in the basic laboratories need to realize their dependence upon a high level of performance amongst those who develop and apply their ideas to sick people. As we shall no longer be able to afford the poorly authenticated ideas of enthusiasts there is a danger that good ideas may be rejected if they are not

properly tested. We must become more efficient without choking the spark of originality and that may involve a willingness to take risks in the development of promising new ideas. The greater difficulty of taking new chemical structures into study in man because of the need to meet very detailed safety requirements has reduced the chance of useful 'surprises' arising in clinical therapeutic research.

Fortunately the spark still burns brightly. The challenge to intellect and compassion posed by the suffering of sick people is an extremely powerful source of motivation. Morale is high and the prospects for really worthwhile advances remain good. The state of the biological sciences is comparable to that of engineering and chemistry a hundred years ago. We have discovered the steam engine but still not the jet. There will be a time of diminishing returns, but not yet.

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