HOLES IN THERAPY

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It is not so much that there are lacunae in our present therapeutic armamentarium. Rather, the world of the clinic should be regarded as a vast desert of uncertainty within which there are only oases of rational treatment. From the very beginnings of life, when unpreventable premature labour may lead to the birth of an unviable foetus, until old age with its increasing dependence on prostheses and when aphasia, paralysis and incontinence threaten countless indignities, there are endless opportunities for the development of effective methods of treatment. Many will require the greater understanding brought about only by research. We urgently require new antiviral agents, as well as new substances that can counter resistance in either bacteria such as staphylococci or parasites like malaria. Our treatment of many forms of cancer remains inadequate. We are making a start in the prevention of genetic conditions but so much more remains to be done. We can do little for crippling forms of joint disease and we have no treatment for intestinal conditions such as Crohn's disease, an ever-increasing affliction of the young. Above all, we are relatively powerless in dealing with the burden placed upon families and whole communities by the problems of anxiety, depression and other forms of chronic mental illness. Furthermore, we are remarkably ineffective in preventing illness produced as a result of human frailty – for example the problems of alcohol abuse, cigarette smoking, the misuse of drugs, overeating, sexually transmitted disease, or the accidents associated with the erratic driving of fast cars.

The most dangerous moments of one's life are those immediately following birth. These moments are immensely more fraught with hazard in infants born prematurely. We have little idea at present of the causes of premature labour but there is no doubt that if we understood more about the mystery of how labour starts, we might be able to devise methods of controlling its onset. The prevention of prematurity would do more than anything else to reduce infant mortality, so tragic to so many parents. Furthermore, whilst the bewildering technology of neonatal intensive care units has done so much for infants born prematurely, the development and staffing of such units present grave problems to health services chronically short of resources and, resembling as they do the cockpit of a Boeing 747, they must be regarded as only a temporary technological expedient for dealing with a major human problem.

As a result of the scientific explosion that has followed the elucidation of the genetic code, and the introduction of methods of analysing the human genome, we are now in a position, unparallelled in human history, to diagnose and prevent a variety of genetic diseases. The

genetic basis of many haematological disorders has been carefully analysed at a molecular level and diseases of collagen synthesis, muscular dystrophy, cystic disease of the kidney, and Huntington's chorea, to mention but a few, are yielding to the same approach. Genetic diseases like cystic fibrosis are on the verge of solution and even common conditions such as diabetes and heart disease, whose inheritance is likely to be polygenic, are now being analysed in this way. We can diagnose many genetic conditions *in utero* using the techniques of placental villous biopsy and therefore advise families on the course of action open to them, particularly whether pregnancy should be terminated, a subject that faces us all with perplexing ethical dilemmas. For the future, however, the major question is whether we shall be able to correct genetic disorders by transferring the missing gene to human beings, as has already been achieved in animals. I have little doubt that this will prove to be a feasible approach to the problems of genetic disease in man, providing, at least initially, that the correction is made to somatic cells and does not create the uncertainties that might result from affecting the germ line.

In the period immediately following the last World War, there was a widespread feeling that infectious diseases had been conquered. After all, we could prevent smallpox with vaccination and we have now, through the good offices of the World Health Organisation, totally eliminated that once terrible scourge from the world. Other viral illnesses such as measles and yellow fever can be similarly controlled. Many of the ancient pestilences of Europe have either disappeared spontaneously, like plague, or been controlled by immunisation, for example diphtheria, or by sanitary measures, as in the case of typhoid fever or cholera. The viruses of influenza, glandular fever and poliomyelitis have all been identified even if vaccines have not been developed in every case. The introduction of antibiotics, and of effective antiparasitic drugs, particularly against malaria, led many to believe that mankind no longer had much to fear from infections. Effectively, with modern science and technology, man felt he was in command of his environment and the apparantly random eradication of whole families, which occurred with plague through the ages and which came again with the pandemics of cholera of the 19th century, were only memories of a tragic past. The events of recent decades have shown how complacent that view was. No one should ever underestimate the capacity of infectious diseases to reassert themselves. We have been alarmed by the emergence of Legionnaire's disease. The development of resistance by bacteria such as staphylococci or parasites like malaria has rendered so-called wonder drugs ineffective. And the advent of AIDS confronts us with an epidemic, particularly in Africa, to rival that produced by the Great Pox when it ravaged Europe after Columbus' return from the New World in 1493.

We urgently need new drugs for the treatment of viral diseases, particularly those due to retroviruses such as appear to be responsible for

AIDS. Yet there are many other as important potential uses of effective antiviral drugs. At present we are unable to produce economically viable vaccines against influenza, since the virus has a remarkable capacity to change itself by mutation, and we therefore need some method of treating a disorder which frequently affects so high a proportion of our populations. Perhaps more importantly, the viruses responsible for the common cold have now been identified and it should be possible to devise methods of treating those runny noses, the result of the commonest infectious disease with which we are afflicted. It is now reasonable to hope that the receptors in the human nasal epithelium that bind to the virus will be identified. Agents may then be synthesised that are capable of preventing this binding, thereby controlling symptoms which remain as unpleasant as they are socially disagreeable.

Cardiovascular disease remains the major killer in the western world. So far as coronary heart disease is concerned, the question as to whether new drugs have played any role in the remarkable reduction of mortality in countries such as the United States in recent years remains enigmatic. There is little doubt that ß-blockers have greatly improved the outlook for patients suffering from coronary insufficiency and the new drugs which reduce blood cholesterol levels promise to prevent acute attacks of coronary occlusion. Furthermore, the use of clot-dissolving drugs, such as streptokinase, appears to be effective treatment of heart attacks in the acute phase of the illness even if the expense is considerable. In the longer term, however, the major questions are how to prevent the development of atheroma in blood vessels, and how to get rid of it once it has occurred. The taking of aspirin appears to be merely a stopgap in preventing thrombosis, however effective, and what is needed is some way of actually dissolving atheromatous plaques, particularly in the coronary or cerebral vessels. Whether there are agents that will do this after oral ingestion, or whether some other substance could be perfused through the entire system from time to time are questions for the astrologist rather than the scientific clinician.

There are other cardiac conditions in which we remain relatively powerless and must resort in the last resort to cardiac transplantation. Disorders of cardiac muscle and of the blood vessels of the pulmonary circulation may require either a fresh heart or a combined cardiac and lung transplant. The problems of organ rejection have been considerably helped by the development of drugs such as cyclosporin but there remain major difficulties in matching donor and recipient to which new immunosuppressive agents, without side effects, might make an important contribution.

Apart from cardiovascular disease, cancer in all its manifold forms remains one of the major challenges to medical research. At present, the use and application of the new techniques of molecular and cell biology are revealing how cancer cells grow and develop, in ways that were unthinkable a few short years ago. Furthermore, modern imaging techniques have made the human body virtually transparent so that it is now

possible to detect tumours, and their spread, with remarkable accuracy. These developments, together with the use of drugs coupled to substances which will home in on tumour cells, have already revolutionised the treatment of certain forms of cancer in recent years. But so much remains to be done. We need a whole range of drugs, comparable to the antibiotics, which will selectively damage and kill cancer cells without affecting the normal cell population. Furthermore, in leukaemia, although the outlook particularly for children has been transformed in recent decades, the disease remains obstinately fatal in a proportion of cases. We still need to know whether viruses produce leukaemia in man, as they do in certain animal species, and whether therefore suitable antiviral agents would be a better form of therapy than the shotgun regimes of antimitotic agents, combined with radiotherapy and bone marrow transplantation, which are such an ordeal for so many patients. There are also many common forms of cancer in which we have made remarkably little progress through the years. Breast cancer is an ever-present hazard for many woman and cancer of the colon remains a major killer in the western world. There is, furthermore, no confirmation that the consumption of a high fibre diet will prevent this modern scourge. In prevention, we could surely do better in controlling cancer of the cervix and in encouraging the eradication of smoking we must be firmer in our attitudes to European Governments. It is in fact remarkable that a British Government should have chosen to do battle with the European Commission on the question of whether to have stern warnings on cigarette packets, which would surely be more effective than those mild admonitions with which the tobacco industry in Britain is currently so content.

Yet it is in psychiatry that the physician must surely feel more helpless than in any other discipline of medicine. Mental illness is one of the greatest problems besetting Health Services throughout the developed world, demanding a huge commitment of resources, both financial and emotional. We know something about the handicap produced by Down's syndrome, but the remainder of mental handicap, unless genetically determined, presents questions that we have scarcely begun to answer. All we can do is to provide as best we can for the life-long support that unfortunate sufferers require. In the psychoses, which include conditions such as schizophrenia and manic-depressive states, we have made some progress using drugs such as lithium but for the most part these illnesses present social and clinical problems with which we wrestle and contend rather than solve or cure. There is perhaps some hope for the future in the advances that are currently being made in the basic sciences of neurobiology, and studies of the brain in schizophrenia have demonstrated pathological abnormalities that were unsuspected by earlier generations of psychiatrists. But we are still faced with illnesses that can destroy families, demean individuals and damage social relationships as no organic illness can ever do. We urgently need to know more about the normal function of the brain and how it is dis-

ordered in these tragic conditions. We must know whether it is in least bit possible that viruses are involved, since if they are, the prospect of vaccine development would provide a way ahead. And we need to know more about the promising developments in analysing the genetic basis of schizophrenia that may permit us to understand more about its inheritence. I have to confess to being one of those who, like Sir Peter Medawar, does not believe that psychoanalysis has made any effective contribution to the treatment of mental illness. For anyone involved in the pharmaceutical industry, the development of any drug to help these most unfortunate sufferers in any community is the greatest of prizes.

The development as the years go by of Alzheimer's Disease may present problems of an almost equally disastrous nature, although mercifully most individuals afflicted have lived productively in the earlier part of their lives. It ranges in severity from the mild condition suffered by a friend of mine – who told a lady one afternoon that he had Alzheimer's Disease. 'Yes,' she replied, 'you told me that this morning' – to the debacle of total cerebral disintegration, a situation in which tragically *mens insana* is so frequently associated with *in corpore sano*. There are at present important scientific developments which are throwing light on this unfortunate condition but despite encouraging reports in the newspapers, there is no evidence that techniques such as foetal brain transplantation will do anything for the condition, which we remain powerless to treat.

The problems of anxiety and depression have a rather better therapeutic record than other forms of mental illness. Nevertheless the addictive and other side effects of the benzodiazopines have somewhat blunted their reputation. At present, the treatment of anxiety seems likely to involve a greater degree of reliance on psychotherapeutic techniques than hitherto.

Diseases of the musculoskeletal system present as great a therapeutic problem as any we have discussed so far. We still know nothing of the cause of progressive muscular atrophy nor have we any effective treatment for this distressing malady. Rheumatoid arthritis can be helped considerably by modern management with drugs and physiotherapy but we still do not know why it occurs, nor why it so frequently affects young women, and our treatment remains symptomatic only. Any clinician will recall patients with chronic deforming arthritis of hands and other joints who have been treated through their lives with all the passing therapeutic fashions, from liver and the removal of teeth on acount of supposed 'focal sepsis' half a century ago to the modern era of steroids, gold and nonsteroidal anti-inflammatory drugs – with virtually no effect on the progression of their disease. We urgently need to know what it is that so destroys the cartilage and bone in joints, just as we also require treatments for osteoarthritis which might do away with the necessity for joint replacements, so much a feature of the waiting lists for surgery in the British National Health Service.

Osteoporosis is a disease, predominantly of the elderly, for which solu-

tions and aetiologies have repeatedly been suggested but which remains a major problem, particularly for post-menopausal women. There is evidence that supplementary oestrogen therapy may prevent progression but the disorder continues to be a major challenge to the metabolic physician. And fractures of the neck of the femur in elderly women still defy analysis, often necessitating prolonged periods in hospital and the services of a wide range of medical and nursing staff.

So many of the disorders for which we require treatment are those which affect the more senior of our citizens. For some such afflictions, for example enlargement of the prostate gland, there are appropriate surgical procedures which relieve the condition. Yet how much more convenient it would be if there were a drug which taken by mouth would result in shrinkage of the enlarged prostate without reducing sexual activity. The gland has always been unfortunately placed at the outlet of the urinary bladder. One of my professors used to give a lecture on how the Almighty might on reflection have redesigned the human body. He concluded that the prostate gland could well have been better placed than where it is.

There are so many other disorders for which we have only partial answers, even if a fair proportion of sufferers can be considerably helped by current methods of treatment. We can do so much for patients with diabetes mellitus, thanks to the discovery of insulin and its more recent production by the techniques of genetic engineering, but we are still relatively ineffective in dealing with the more serious complications such as renal disease, ocular involvement or degeneration of the nervous system. We can now treat the very common condition of peptic ulceration with considerable success as a result of the development of the H2-receptor antagonists but we are still uncertain whether we have effectively reduced the overall mortality of bleeding from peptic ulcers. Treatment of thyrotoxicosis is now relatively simple using currently available antithyroid drugs, but we continue to face formidable problems with the ocular abnormalities and paralyses which may plague individuals so afflicted. We have yet to unravel why autoimmune reactions seem to cause the condition, just as we still lack any knowledge of why the lung may sometimes be progressively destroyed by fibrosing alveolitis, another condition thought to have an automimmune basis. In asthma, there have been great advances in treatment with modern aerosols but for reasons unknown, we still lose a proportion of patients with asthma, particularly in adult life.

In disorders of the central nervous system, there are now a number of conditions which may be effectively, if not completely, treated. Parkinson's disease is perhaps the best example of a chronic disease of the central nervous system which, thanks to therapeutic advances, may now be considerably relieved by drugs. Yet there are many others where we remain ignorant and often powerless. No one can fail to be distressed that we still have no understanding of the cause of multiple sclerosis and despite attempts to treat the malady with fatty acids, steroids or immunosuppression, no effective treatment has yet emerged.

There are other conditions, often affecting younger people as multiple sclerosis does, that have as yet defied the efforts of generations of research workers. Crohn's disease has become distressingly frequent in northern Europe and in the United States in the past three decades, causing untold distress to its sufferers. Again, we have no knowledge of why it occurs and sadly no effective treatment. Ulcerative colitis has a similarly obscure origin and in severe cases can only be treated by total colectomy.

Yet it is in the treatment of disorders that are due to the fundamental frailty of human behaviour that we have failed most. It is a feature of the modern world that the pursuit of happiness, so much recommended as one of the rights of man in that Utopian document, the American Declaration of Independance, should have been widely misinterpreted as the right to the pursuit of pleasure. It is to this that we owe the social calamities that we face in so many western countries as a result of the use of addictive drugs for personal gratification, with such disastrous results. To this may be added the widespread distress associated with the abuse of alcohol. Theoretically, cancer of the lung due to smoking should not occur, yet it apparantly takes a full course in medical school to educate people that cigarette smoking is a social evil with lethal consequences not only to the lung but also to the cardiovascular system. Too many people in western society are overweight, too many have treatable high blood pressure and too many enjoy driving fast cars with such abandon that they overload the accident and emergency services of our hospitals, particularly when they have been drinking alcoholic beverages. All of these problems are theoretically preventable, as are the hazards of sexually transmitted diseases, particularly AIDS. With no treatment available and no vaccine yet developed for the AIDS epidemic, we are left only with education and the technology which allows the production of reliably thin and strong sheets of rubber to prevent this catastrophic disease. At present our techniques of health education are in their infancy and they urgently need greater attention and greater resources.

This account may perhaps seem to be unduly pessimistic. You asked me, however, to say something about the serious limitations of our present therapy and I have done so. But despite the many lacunae in our therapeutic armamentarium to which I referred at the beginning of this talk, there is a great deal that we can now do to help our patients, thanks to the prodigious efforts of many scientists and clinicians working patiently in laboratories in industry just as much as in the clinic or in the cloistered halls of academe. There is so much more to do – but I am sufficient of an optimist, and all scientists must be optimists, to believe that the future holds out great hope. Those oases of rational treatment will surely conquer that vast desert of uncertainty with which we began.