

**SCIENCE
IN MEDICINE:
HOW FAR HAS
IT ADVANCED?**



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Introduction

Professor George Teeling Smith

The chapters in this book are based on contributions to a seminar organised jointly by the Office of Health Economics and the International Science Policy Foundation, and held at the Royal Society of Medicine in London on 10 December 1992. An account of the discussion which followed each paper is also included. Background notes were circulated to the participants in advance of the meeting and this introduction is largely based on those notes.

It was pointed out that until the start of the twentieth century, medicine had been practised largely as an art. The classical 'controlled trial' of the use of limes to prevent scurvy in the British navy and the elaboration of the germ theory by Pasteur, for example had been isolated examples of scientific method applied to medicine. Generally, medicine was taught didactically based on traditional beliefs.

However, these two early examples of science in medicine well illustrate the two aspects of scientific investigation which have characterised the development of medicine in the twentieth century. The first is the systematic evaluation of outcomes of different types of treatment. The second is the elucidation of the underlying causes of disease, leading in turn to systematic methods of prevention and treatment.

On evaluation, when Cochrane wrote his seminal book* twenty-one years ago, his was still largely a voice crying in the wilderness. The pharmaceutical manufacturers had fully adopted the principle of the randomised and usually 'double blind' clinical trial: but for other aspects of medicine and surgery there was little general acceptance that procedures should be scientifically evaluated before they were adopted — or, more often, continued — in routine clinical practice. It is only since then that the principle of routinely evaluating outcomes of medical and surgical procedures has become more generally accepted. It is probably no longer possible, as it was for Cochrane twenty-one years ago, to quote words from Eliot's play 'The Family Reunion' as being typical of much medical practice:

'Not for the good that it will do
But that nothing may be left undone
On the margin of the impossible.'

Turning to the underlying evaluation of the causes of disease, very much has been achieved this century. The early work of Barger and Dale at the Wellcome Foundation, showing the chemical nature of the transmission of nerve impulses, is often quoted as an early example of the scientific investigation of bodily functions which could become disordered. Much more recently, advances in molecular biology are likely to solve many of the still unsolved puzzles in relation to the cause of disease.

**Effectiveness and Efficiency: Random Reflections on Health Services*. Nuffield Provincial Hospitals Trust, 1972

Introduction

The chapters in this book examine these two aspects of science in medicine, starting with a historical perspective, and then taking three examples — infection: nervous diseases: and psychiatry — to illustrate the advances of science in medicine in the twentieth century. The examples have been chosen to illustrate different degrees of penetration of the scientific method in different fields of medicine.

Finally, the roles of molecular biology and social science are considered. The objective is to assess how far science has already influenced the practice of medicine and its teaching, and to consider how scientific methods could be more fully exploited in the practice of medicine to make it more 'effective and efficient' (in Cochrane's classic words).

Each of the authors' contributions, together with the discussion which followed their presentation, clearly illustrates the way in which science has indeed contributed to modern medicine. There is also invaluable discussion of how the contribution of science could be developed in the years ahead. In so far as the book signposts the way forward, it is a fitting tribute to all those such as Archie Cochrane who have done so much to make medicine a twentieth century science.

Attendance list

Dr Alan Bailey	Dr Ann Hale
Dr E. D. Barlow	Dr Philip Hopkins
Sir Douglas Black	Dr John Horder
Professor Martin Bobrow	Dame Rosalinde Hurley
Dr David Budworth	Dr Jeff Kipling
Dr Iain Chalmers	Mr Alan Mayne
Mr Henry Connor	Ms Cynthia Roberts
Mr Robin Fears	Dr Lesley Rogers
Professor Hugh Freeman	Dr Craig Sinclair
Mr J. V. Gimpel	Dr Josephine Stein
Mr David Godfrey	Mr Richard West
Miss Jane Griffin	Dr Peter Woodford
Dr John Griffin	

Historical background: Medicine as dogma

Professor William Bynum

‘There is nothing in which a young practitioner should be more on his guard, than being misled by the sweeping dogmas of schools, and the indiscriminate practice of sects, or of favourite practitioners.’ So wrote Sir Gilbert Blane in his *Elements of Medical Logick*, first published in 1819. Despite his injunctions, a young beginner might have done worse than take Blane as a model of a favourite practitioner, for Blane’s career had all the trappings of contemporary success and modest but secure posthumous fame: physician to the fleet, to the Prince of Wales, later George IV, to St Thomas’s Hospital; FRS; a baronetcy; an important role fifty years after James Lind in the final acceptance by the British navy of the value of citrus fruits in the prevention and treatment of scurvy among British sailors; and an equally significant position in the introduction of systematic record keeping in British medicine.

Chronologically, Blane falls midway within a tradition of British clinical medicine which is the subject of this essay. It stretches from Thomas Sydenham through John Coakley Lettsom and William Heberden in the eighteenth century, Peter Mere Latham and Thomas Watson in the nineteenth, to Samuel Gee and Thomas Horder in the late nineteenth and twentieth. Broad-church in its composition, the tradition rested on shared assumptions which transcend the vastly different social and intellectual contexts within which these individuals plied their skills with such success. These men may be linked by a common approach to medical knowledge as empirical in its origin and practical in its application. The tradition should not be seen as naively anti-scientific, though occasional individual pronouncements cast doubt on the application of experimental findings in clinical settings; nor should it be castigated as dogmatic, since dogma within medicine was one of the tradition’s bugbears. Consequently, the title of my paper might better be ‘Medicine as Experience’; or possibly even ‘Science as Dogma’.

Nevertheless, by way of historical prelude to the main theme of this volume, it is worth explicating the values which I see within this clinical tradition. I shall be discursive and sometimes a-historical, in yoking together practitioners widely separated in time and context, but I hope that the result might help us understand why the historical partnerships of science and medicine, knowledge and practice, have never been straightforward.

Here are five characteristics which help define this clinical tradition:

1. Worship of Sydenham;
2. Primacy of doctor–patient encounter;

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3. Emphasis on systematic observation;
4. Suspicion of theory, from whatever source;
5. Medical practice as an individualistic art.

In what follows I should like to examine some of the salient features of each of these attitudes.

The veneration of Sydenham, the English Hippocrates, has been so widespread that it might seem inappropriate to count this as one of the hallmarks of any tradition. His works continued to be printed throughout the eighteenth century and were edited and translated with loving care by Robert Latham in the nineteenth, in a series which was published by a society which bore Sydenham's name.

At least some of those who praised Sydenham read him, and those who did would have noticed that Sydenham's prescriptive vision of medicine's present and future was that of a craft activity with little use for what we call the basic sciences.

In a series of memorable passages, he likened medicine to shoe-mending; praised the talents of butchers over anatomists; disparaged the medical education on offer at the English universities; dismissed virtually the whole of medical literature; and proposed that the practice of medicine was most soundly based when it consisted of only three activities: the careful description of nosologically distinct diseases; the application, more or less through trial and error, of remedies for these diseases; and the hope that more specific remedies of the type of Peruvian bark for intermittent fevers would ultimately be discovered. Sydenham never believed that the practice of medicine was as simple as cooking; he did however hold that the ministering doctor need have no more idea why a drug produces a sweat or a purge than a cook need know why cooking tenderises meat.

Sydenham's historical reputation was probably greater than his immediate one, though he was virtually canonised within a year of his death when John Locke grouped Sydenham with Robert Boyle, Christiaan Huygens and Isaac Newton in the preface to Locke's own monumental *Essay Concerning Human Understanding* (1690). Locke described these four as the master-builders of his age, Locke himself being content to be 'employed as an under-labourer in clearing the ground a little, and removing some of the rubbish that lies in the way to knowledge'. Also just after Sydenham's death, on the Continent, Georgius Baglivi spoke of Sydenham as 'the embellisher and ornament of our profession', and Hermann Boerhaave coupled the English Hippocrates with the original one, so ensuring the vigorous afterlife of the Puritan cavalry officer, to whom Samuel Gee more than two centuries later was to dedicate his *Medical Lectures and Clinical Aphorisms*.

While Sydenham was observing, his almost exact contemporary Thomas Willis was experimenting: in chemistry, physiology, pharmacology,

comparative anatomy. Not doing just that, Willis was also busy seeing patients, and attempting to relate his astute clinical observations on a wide range of neurological, neuromuscular, metabolic, cardiac and respiratory diseases to his experimental enquiries: attempting, in short, to relate the corpuscular natural philosophy of the period to the bedside. At the time of Willis's death in 1675, both his British and his European reputations exceeded those of Sydenham, his works were translated into English as *The Practice of Physick* and the original Latin *Opera Omnia* found much favour on the Continent.

Yet, within a few years, Willis's works had lost their contemporary currency, with only a couple of further editions, compared to some forty eighteenth-century editions of Sydenham, in Latin, French, German, Dutch, and, repeatedly, in English. Sydenham became a symbol for several reformist groups in medicine, Willis largely forgotten. Until recently, the only modern biography of him was by a Swiss neurologist and had been originally published in German.

Part of the reason for this divergence in their posthumous fames is easy to find, and it is not simply to do with their literary styles, or the fact that Sydenham presented himself as the originator of unprejudiced, naked observations. We sometimes seem to think that our generation has been the first to recognise that observations are inevitably theory-laden. William Cullen, yet another admirer of Sydenham, knew better. He wrote a century later:

'Every one nowadays pretends to neglect theory, and to stick to observation. But the first is in talk only, for every man has his theory, good or bad, which he occasionally employs; and the only difference is, that weak men who have little extent of ability for, or have had little experience in reasoning, are most liable to be attached to frivolous theories.'

Cullen would, I think, have correctly included Sydenham in his list of the theorist *malgré lui*, though of course for many Sydenham was theory-free, the quintessential medical Baconian empiricist.

These reasons are important, but a more cogent explanation of Sydenham's historical appeal lies in his call for a kind of medical democracy. His was an open invitation for all ambitious doctors to participate in the medical enterprise, through the medium of the doctor-patient encounter. The history of medicine is filled with reformers wishing to reform the faculty, to rid medicine of its esoteric, elitist character. A pupil of Cullen, William Buchan, for example, pioneered the self-help manual, seeking to 'lay medicine open' so that through reading his phenomenally popular *Domestic Medicine* (1769), every man could be his own doctor.

Sydenham's strategy was different, preserving the distinction between doctor and patient, yet emphasising those very skills of diagnosis and treatment whereby every doctor earned his bread and butter. He defined medical science in such a way as would allow every doctor to participate,

even (or maybe even especially) those trained by what was the common way until well into the nineteenth century, the apprenticeship. Willis was cerebral, intellectual and sometimes opaque; Sydenham was clear and practical, locating his medical epistemology within the business of medicine, i.e. seeing patients. Every doctor could imagine he had had as his own patients such as Sydenham described, whereas the case histories of Willis are filled with pathophysiological comments on the causes of the patients' signs and symptoms, and often, with autopsy findings as well. There are only a couple of references to casual autopsies in the whole of Sydenham's writings. His setting was always the ordinary: the surgery, the bedroom, the sitting-room, never behind the scenes.

Historians have characterised medicine before the nineteenth century as patient dominated, with diagnoses based largely on the patient's own description of his disease and treatments oriented towards patient demands and expectations. Patients and their doctors tended to share a common vocabulary and even a common cosmology, and the relatively low social status of medicine as an occupation meant that patients often controlled the relationship. Sydenham as a clinical observer often went beyond anything the ordinary patient might have noticed about the timing, course, signs and symptoms of his illness, but the encounter with him would not have involved esoteric procedures or vocabulary. 'The public are our employers, and, in the long run, we shall be what our employers make us', the successful ophthalmic surgeon Robert Brudenell Carter wrote early in the twentieth century, in an age of medical science. He had a point: willy-nilly, most doctors have always spent most of their professional time responding to the particular, sometimes urgent, needs of those they serve. No wonder a philosophy of medicine which made that doctor-patient encounter so central had such wide and lasting appeal.

But, if for Sydenham and his followers, medicine was essentially an observational and manipulative activity, it was also, in its highest form, to be a systematic one. Sydenham distilled many separate observations into his vivid depiction of diseases such as smallpox, measles, gout and hysteria. He also developed a kind of proto-epidemiology, through his notion of the epidemic constitution and his concern with prevalent diseases in individual years or seasons. He gives us few hints about the written form his individual case notes took and his raw data, such as they were, have long since disappeared. Nevertheless, he made the observation of individuals and epidemics so crucial to his medical life that it is not surprising that his authority was often invoked by those wishing to make medicine more empirical and observational.

Once the medical periodical begins, from the middle decades of the eighteenth century, the typical publication is the case history. For long the dominant form was the single case history, usually with a successful

outcome which did credit to the diagnostic and, especially, therapeutic skills of the author. Far more account books than case books survive for eighteenth and early nineteenth-century practitioners, probably indicative of the relative importance of financial and cognitive matters for most doctors. In the published periodical and monographic literature, however, there was a gradual shift from single to multiple case reporting, and an increasing willingness, typified by William Withering's *Account of the Foxglove* (1785), to include therapeutic failures as well as successes. Naval and army doctors such as James McGrigor, Thomas Trotter and Gilbert Blane were active in this movement towards what was called the 'Quantification of Experience'. This is not surprising, since public money was involved in treating soldiers and sailors, and a sick army could not fight. Blane in particular was involved in introducing these methods into civilian hospital practice, publishing yearly statistics for St Thomas's Hospital and encouraging all medical institutions to provide annual statements of patient numbers, diseases, therapies and outcomes. With the increased presence of medical students clerking on hospital wards, hospital case history became more formalised, and medical students in end-of-year addresses were exhorted to continue the habit of systematic observation in their after-lives. Some at least did. 'Observation runs sadly to waste when it is made upon cases piecemeal', wrote Peter Mere Latham, in his lectures on *Diseases of the Heart* (1845).

By the early nineteenth century, the rituals of physical diagnosis were beginning to acquire a modern feel, especially after the popularisation of percussion by J.-N. Corvisart in 1806 and the published introduction of stethoscopy by Laennec in 1819. This French 'hospital medicine' attracted students from all over the western world, and although a new emphasis on lesions, gross pathology and solidism replaced the humoralism which had characterised Sydenham's work, hospital medicine can still be seen as falling within the Sydenhamian tradition. For Pierre Louis, for example, one of the high priests of this new form of hospital practice, the *méthode numérique* was but a statistical way of effecting Sydenham's *methodus medendi*.

The hospital medicine of the early nineteenth century revolved around the axis of the ward and the morgue, and in that sense was broader than Sydenham's, with his contentment with the parlour or bedside. But, as with Sydenham, its observational foundations were supposed to protect it from the seepage of vain theory. Locke and Sydenham were suspicious of the microscope, with its power to magnify distortion and encourage speculation about essences. So, despite Bichat and his handlens, were the French clinicians. Chemistry and physiology were commonly referred to as the accessory sciences, rather than the basic ones, and exponents of hospital medicine looked upon these sciences as sources of the speculative tendencies which had bedevilled the medicine

of the old regime. Laennec was content to describe the course and consequences of phthisis or consumption: the cause of the disease would, he avowed, be forever hidden from us.

Early nineteenth-century reformers viewed many of the efforts of their academic predecessors as hopelessly theoretical and speculative. 'I have lived myself to see the disciples of Hoffmann, Boerhaave, Stahl, Cullen, Brown succeed one another like the shifting figures of a magic lantern, and their fancies, like the dresses of the annual doll-babies from Paris, becoming, from their novelty, the vogue of the day, and yielding to the next novelty their ephemeral favor', wrote Thomas Jefferson to Casper Wistar, the Philadelphia anatomist, in 1807. 'There is something fascinating about science', quipped Jefferson's compatriot Mark Twain late in the century. 'One gets such wholesome returns of conjecture out of such trifling investment of fact.'

It is not, of course, that the early nineteenth-century clinicians were against science. Far from it. The most systematic and radically empirical statement of the philosophy of the Paris school was produced in the 1840s by Elisha Bartlett, an American student of Pierre Louis, in a volume entitled *Philosophy of Medical Science*. For Bartlett and many of his colleagues, observation *was* science. The purpose of medical education was to train the senses to see, hear, taste, feel and smell the phenomena of disease.

It was thus not science *per se* but theory and speculation which were to be expunged from medical practice: however, sciences like chemistry, physiology and microscopy could be potent sources of speculation and thus were viewed with suspicion. As Sydenham was reputed to have told the young Hans Sloane: 'No, young man, all that [anatomy, botany, i.e. medical science] is stuff: you must go to the bedside, it is there alone you can learn disease.'

Tension between what we would call the observationalists and the experimentalists is a recurrent theme in the history of medicine: in a sense the Hippocratics represent the former, and Galen the latter, and the demise of Galenism in the sixteenth and early seventeenth centuries was not accompanied by the loss of Hippocratic authority. It was easy for admirers of Sydenham to disparage the achievements of Willis, and even Harvey sometimes got short shrift: Thomas Jefferson commented in a letter to Edward Jenner that Harvey's work was 'a beautiful addition to our knowledge of the animal economy, but on a review of the practice of medicine before and since that epoch, I do not see any great amelioration which has been derived from that study'. Samuel Gee refused the invitation to deliver the Harveian oration to the Royal College of Physicians, insisting 'anatomy, not physiology. In anatomy you have facts; in physiology more or less theory.'

Claude Bernard early perceived the gap between observational and experimental medicine. After all, he had been educated in the Paris hospitals

before turning to physiology, and his *Introduction to the Study of Experimental Medicine* (1865) represented, among other things, an attempt to bridge the gap. Observations, he argued, are the starting point of medical inquiry, whether made in the clinic or the laboratory. But only controlled experiment can produce understanding.

By Bernard's day, experimental medical science was becoming a potent estate within medicine, as physiology, bacteriology, cellular pathology, pharmacology and immunology made their impact on the concepts and capacities of clinical medicine. A few decades ago, this was presented as an undiluted triumph, as germ theory replaced miasmatic ones in the explanation of infectious diseases, aseptic surgery replaced the barbarism of pre-Listerian surgery, vaccine and chemotherapy rendered redundant the heroic therapies of the bleeding, purging and vomiting age; in short, as science replaced empiricism. Historians today are more likely to give equal time to those who continued to be suspicious of medical science as a source of speculation, and to remind that germ theory also gave rise to notions of focal infection and auto-intoxication; that it rendered scientific doctors contemptuous of the citrus-fruit treatment of scurvy since bacteriology seemed to offer a more sophisticated theory of scurvy's causation; or that as surgery became safer it also became more fashionable, and that countless appendices, ovaries, colons, tonsils, kidneys and lives were sacrificed on the altar of scientific surgery.

Late nineteenth-century critics of medical science and of scientifically-enthusiastic clinicians often extolled the art of medicine over its science, the individuality of the patient, and the uniqueness of the doctor-patient encounter. 'Art is myself; science is ourselves', quoted Claude Bernard with approval. Exponents of the clinical art may have agreed, but argued that success in practice demanded more art than science, more experience than theory. Clinical skills could not be taught, they had to be learned, and in that sense, medicine was ever to be a lonely business, the successful practitioner an individualist, at least while at work.

Professor Teeling Smith asked me to discuss medicine as dogma. I hope I have not strayed too far from my brief, in trying to provide some context for understanding why many doctors were not instantly enamoured with the rise of experimental science within medicine in the nineteenth and early twentieth centuries. But it would be anachronistic to view this observational, bedside tradition as anti-scientific: it merely offered another vision and version of medical science.

Of course, medical practice was and is often dogmatic: dictionary definitions of dogma include: 'a settled opinion: a principle or tenet: a doctrine laid down with authority'. The opposite of dogma is doubt, which, according to Claude Bernard, is the great experimental principle: 'that philosophical doubt which leaves to the mind its freedom and initiative'. Sir Thomas Lewis had much the same thing in view when he characterised the different mental attributes which typified the practitioner and the investigator:

'Self confidence is by general consent one of the essentials to the practice of medicine, for it breeds confidence, faith, and hope. Diffidence, by equally general consent, is an essential quality in investigation, for it breeds inquiry. Here then are chief characteristics each necessary in its own sphere, each unsuited to the other. The two irreconcilables do not stand alone but find natural companions.

'A natural companion of confidence is an easy and uncritical acceptance of statements of fact and of hypothesis; it is often coupled with a very wide and diverse acquaintanceship with other men's work and thoughts. The companion of diffidence is skepticism; it tends to be coupled with knowledge less extensive but derived from personal experience and analysis, knowledge more precise and often more fundamental.'

If Lewis was right, the psychological differences between the producers and the dispensers of medical knowledge are considerable; this may help explain why science has not got as far as it might have in medicine.

If doubt is the essence of science, one is reminded that the greatest philosophical doubter of all times, David Hume, confined his scepticism to his study but in company was the most cheerful and sociable of men. Doubt and humility should also have their place at the bedside as well as in the laboratory, and to the extent that more openness and more honesty have begun to characterise the doctor-patient relationship, clinical medicine is taking upon itself two of the most desirable qualities of science.

DISCUSSION

SIR DAVID WEATHERALL: Professor Bynum, would you like to speculate on Sydenham's views on the scientific basis of medicine? He went back to Oxford after the Civil War and was obviously fairly close to the Oxford scientists. Why do you think he broke away in the way that he did?

PROFESSOR WILLIAM BYNUM: I do not know. One is often driven at the end of the day to provide idiosyncratic explanations. Sydenham was an interesting man. The key to Sydenham is to remember that his happiest days were riding in Cromwell's army. Therefore by nature he was somewhat of a rough and ready outdoors man who liked to ride horseback and fight the Royalists. He was not intellectual in the way that people often are for reasons to do with their own personalities and their own psychologies. I suspect that is the situation at the end of the day.

As to his message, I think that he benefited from the way in which it was presented. His writings are full of memorable, quotable images which became part of the folklore of medicine, and in a way a tradition grew up round him. He is always depicted as more or less on the side of the angels. He is such that, if you take the scientifically inclined

Victorians of the early twentieth century, nobody ever said anything bad against Sydenham. You might say that at the time it was absolutely right for him to adopt this attitude, now that we have gone on and achieved something that is more appropriate by way of the amalgamation of experimental and observational skills, but that he was absolutely right and Willis was absolutely wrong in his time.

If you look at Willis's achievements, he had an amazingly bad press — also an Oxford man, of course — but they are formidable. He had a powerful intellect. The thing that I think is remarkable about Willis's writing is that he has a very clear notion of when he is speculating and when he is not. He will often put out: 'Here's *my* theory about the cause of this disease or this physiological phenomenon but I know this is speculation, and if you have a better theory or evidence, let's see it'. He is very open in that. At the same time, however, his writings do ramble: they go on and on and the paragraphs are very long and his vocabulary is pretty strange, so it is difficult to read. Historically it had a half-life much shorter than that of Sydenham, because Sydenham was folksy and homely and the writing was fairly direct and immediate.

In respect of the image, in a way the programme is democratic in its appeal. If you take the people I suspect George Teeling Smith wanted me to talk about — the Brunonians and the people who saw disease as having just one causation (and the theory is very limited: 'Just give opium and alcohol') — there are lots of these movements in the history of medicine which are dogmatic and they appeal because they are not esoteric and everybody can understand them. Sydenham's programme, I think, was universal in that way, and therefore it unified the medical profession, which thought: 'Well, yes, this is great; now I have something I can contribute too', and everyone could become a little Sydenhamian, but nobody could, or even wanted to, become a kind of scientific practitioner.

THE CHAIRMAN (DR MAURICE GOLDSMITH): May we take up another aspect of Sydenham's field of activity — that is, the doctor-patient encounters and medical relationships? I wonder whether anyone here has something particular to say on this?

DR PHILIP HOPKINS: I was delighted to hear your reference to Sydenham and his thinking because it is all the more important today, to recognise the close relationship of the psyche (mind) and the soma (body). The late Dr Michael Balint was a Hungarian psychoanalyst who developed a training system (later to be called Balint Groups) for family doctors to help them to recognise and to use what was happening in the doctor-patient relationship, to help them to understand how emotional problems were related to symptoms. He had started this work in Budapest in the early 1920s, and continued it in this country in the

1950s. In my experience, this psychosomatic approach in medical practice is highly relevant in a majority of illnesses presented by patients to their doctors, and it has had an enormous influence on medical practice throughout the world.

When I first saw the title of this seminar, 'Science in Medicine — how far has it Advanced?' another question came to my mind: Was this intended to mean, how far has science advanced, or how far has medicine advanced? If this referred to science, clearly it has advanced remarkably, fantastically, enormously; if it referred to medicine, we must ask what does this mean, and for how many of our patients? In my experience over many years as a family doctor, I have found that some 4 per cent of my patients need and benefit from the highly scientific advances in surgery, and perhaps another 20 per cent of them from the pharmaceutical advances in the development of antibiotic therapy, drugs for cardiovascular disease, and so on. It is of the utmost importance that we recognise this, and my question must be, how do we put this over in the training of our medical students, our future generations of doctors? From my student days, I remember the emphasis placed on the need for our understanding of pathological processes, to the extent that we were urged to follow our patients into the post-mortem room in order to learn medicine! As it could not be seen, little was said about the importance of the patient's mind. I am sure that I was not alone in taking some years to overcome this attitude, before I could be interested in, and concerned about, my patients as people. I wonder how you feel this should be brought into the training of medical students?

PROFESSOR BYNUM: I am sure that the students who study medical history come out the better for it. It is just those kinds of points that demonstrate the richness of medicine as a social activity. Medicine as different ways of seeing the same sort of creature is something that emerges from the kind of historical insight that we try to give our students.

I am intrigued by your figures. I am sure that Sydenham will be quietly smiling to himself, if he is listening somewhere, that maybe he was right after all!

THE CHAIRMAN: Thank you.

History of science in medicine

Sir Christopher Booth

Clinical medicine has always had an uneasy relationship with science. When Hans Sloane as a young man first met the great physician Thomas Sydenham, he brought with him testimonials to his expertise as an able anatomist and botanist. 'Anatomy, botany, nonsense', said Sydenham, 'go to the bedside — there only will you learn disease'. Sir Henry Dale had a similar experience when he arrived at St Bartholomew's Hospital as a medical student in 1900 — his chief, Samuel Gee, told him in no uncertain terms that he could forget all the physiology he had learnt at Cambridge since medicine was not a science but merely an empirical art.

Nevertheless, despite the reluctance of practising physicians to abandon the dogmas of their day, it has been science, and particularly technology, that have transformed Samuel Gee's empirical art into the medicine of today. The experimental method, so important to this transformation, was a product of the Renaissance. The great Italian artists and anatomists who so much advanced knowledge of the structure of the human body were contemporaries of Sanctorius Sanctorius of Padua who designed a number of ingenious instruments, in particular a highly sensitive weighing machine in which he spent a considerable proportion of his life. By the use of careful techniques of weighing, he was able to estimate the amount of 'insensible perspiration' that occurs in the human body. But it is to William Harvey that we owe not only the remarkable experiments, so simple and so timeless, which established the circulation of the blood, but also a science of medicine out of which, in the words of Sir Thomas Lewis, physiology and pathology were later to be born.

The development of medicine as a science in the modern era, however, had its origins in the nineteenth century. In France, the birth of the clinic was a great stimulus to specialisation in medicine, encouraging the detailed study of specific diseases. It was a development that was not confined to France. In England Richard Bright concentrated his research at Guy's Hospital on diseases of the kidney, pioneering the creation of nephrology as a specialty in medicine. But at the same time important developments were afoot in Germany. The foundation of the University of Berlin by Wilhelm von Humboldt in 1810 stimulated the growth of a university system which set out specifically to encourage scientific research. New sciences basic to medicine — physiology, pathology and later bacteriology — began to grow, and strong university departments in these subjects were soon established, where research was to be all-important.

So far as biomedical science is concerned, it is remarkable how much progress had already been made by the early years of the nineteenth

century. It was established, for example, that life is maintained by chemical reactions of the same nature as those that occur in test-tubes. In 1847, von Helmholtz showed that the laws of conservation of energy applied as much to living tissues as to non-living things. The main ingredients of food — fat, carbohydrate and protein — were identified, and their transformation in the body was studied, although the discovery of the vitamins had to await the next century. Mathematics, too, was found to be an indispensable tool of medical science, physicians such as Pierre Louis in Paris beginning, early in the nineteenth century, to call statistical methods to their aid. Physics was also important, the induction coil, developed between 1830 and 1850, making it possible to make galvanometers of improved sensitivity, recording drums (kymographs) which could assist in the analysis of complex physiological phenomena and even techniques for the study of nerve impulses.

It was also during the nineteenth century, particularly in Germany, that the microscope came into its own. Capitalising on the improvements in microscopy that followed on Joseph Jackson Lister's production of good achromatic lenses, German histologists were able to show that all living organisms are made up of very small units or cells, not visible to the naked eye. In disease there might be specific disorders of these cellular elements. By 1858, Rudolf Virchow, in his great work *Die Cellularpathologie*, was able to demonstrate a whole new concept of human disease based on disturbances of the cellular structures of the human body.

The microscope was also of vital importance in the emergence of bacteriology as a new science. That remarkable Dutchman, Antoni van Leeuwenhoek of Delft, had observed tiny organisms with his primitive instruments in the first decades of the eighteenth century, but the work of Louis Pasteur in France and of Robert Koch in Germany, supported by brilliant contemporaries in other countries such as Britain, established the science of bacteriology. From 1875 onwards, a whole range of human diseases was found to be due to infection by specific microorganisms.

These scientific developments led to profound changes in the structure of universities and in attitudes to research. In addition to departments of chemistry and physics, new departments in the new sciences of physiology, pathology and bacteriology were created, particularly in Germany. Research institutes were also being set up, popular subscription building a research institute for Louis Pasteur in Paris, and in Germany the government provided special laboratories for Robert Koch and for the great pathologist, Paul Ehrlich. In England, an institute was named after Joseph Lister, the pioneer of antiseptic surgery and the son of Joseph Jackson Lister, and in Japan facilities were provided for Shibasaburo Kitasato, co-discoverer of diphtheria antitoxin with the German Nobel Laureate, Emil von Behring.

By the end of the nineteenth century, there had been a great burgeoning of the sciences basic to medicine. For the future, it was highly significant that

in the latter part of that century, young Americans flocked to the laboratories and clinics of the German medical schools and research institutes, just as earlier in the century they had visited the clinics in Paris, where the influence of the physiologist, Claude Bernard, was later preeminent. America soon began to emulate these new European traditions by establishing basic science laboratories in the universities and medical schools. The laboratories of physiology at Harvard, Yale and Johns Hopkins were all founded as early as the 1870s.

At the same time there was a great expansion throughout the United States of new medical schools, among which Johns Hopkins, staffed by men steeped in the German tradition, was preeminent. A further development of great significance in the United States was the foundation in 1904 of the Rockefeller Institute for Medical Research in New York City, which was unique in being associated later with its own hospital for clinical research. The institute was to have a vital influence on scientific medicine in the United States. It was here that Rufus Cole, translated from Johns Hopkins, was to recruit Oswald Avery who, with his colleagues, later made the crucial discovery that the genetic material in bacteria is DNA.

Yet, although there had been no hesitation in creating university departments in the basic sciences directed by full-time professors employed and paid by universities or research institutes, there had been by the end of the nineteenth century little comparable development in the world of clinical practice. The care of patients and the teaching of students in medicine occupied the time of the clinicians almost wholly, and they were remunerated partly from student fees as well as from their work as private practitioners. In Germany, however, clinical departments were beginning to have their own laboratories and assistants, even though the professors often maintained large private practices. But the development of clinical science carried out in clinical departments by men and women devoted to research and working with patients in a clinical setting was to be a twentieth-century phenomenon which, during the early years of this century, was to develop and later reach its fruition in the United States.

The most influential individual to encourage this development was the remarkable German physiologist, Karl Ludwig, with whom so many young Americans received their early training in medical science. Karl Ludwig argued that research in the clinic would flourish better in the free environment of the United States than in the German schools where the *Geheimrat* system tended to inhibit the ambitions of the young.

The question must be asked: how effective has the American organisation of university-based clinical research been? One cannot analyse the enormous output of clinical departments in American universities, often published in the *Proceedings of the Association of American Physicians* or in

the *Journal of Clinical Investigation*, but at the highest level it is possible to examine the record of American clinical investigators in winning Nobel prizes. In 1934, G. R. Minot and W. P. Murphy of Boston, together with the pathologist George Whipple, won the prize for their work demonstrating that pernicious anaemia, then a universally fatal disease, could be successfully treated with a liver diet. R. F. Cournand and D. W. Richards received the prize for their pioneering work on cardiac catheterisation, C. B. Huggins for the treatment of prostatic cancer with hormone therapy, P. S. Hench, with his scientific colleague E. C. Kendall for the introduction of steroid treatment, Rosalyn Yalow for the development of the technique of radioimmunoassay and M. S. Brown and J. L. Goldstein for their work on the molecular basis of lipid metabolism. In 1966, D. Carleton Gajdusek won the Nobel prize for his demonstration of the importance of slow viruses in chronic diseases of the central nervous system, particularly kuru, a disorder associated with ritual cannibalism in New Guinea. More recently, Murray and Thomas have been rewarded for their introduction of transplantation of kidney and bone marrow. Of these, all but Huggins were members of the Association of American Physicians, founded as early as 1886 and providing a forum within which, from the start, basic scientists and clinicians could discuss their problems together.

By contrast, the only clinicians from other countries to have won Nobel prizes have been a Canadian surgeon, Frederick G. Banting, for his contribution to the discovery of insulin and the German surgeon, W. Forssman, who first passed a catheter into his own heart and who shared the prize with Cournand and Richards. In 1903, Nils Finsen, a Dane, won the prize for suggesting that light was important in the treatment of lupus and smallpox, an avenue of research that has not fulfilled its early promise. The Swiss surgeon Emil Theodor Kocher was rewarded for his work on the thyroid gland. Egas Moniz, Portuguese physician, received the accolade for introducing cerebral angiography and, more dubiously, for his advocacy of prefrontal leucotomy. The pragmatic observation that malaria inoculation might be useful for the treatment of dementia paralytica won the prize for Julius Wagner-Jauregg of Austria in 1927. If one excludes Sir Ronald Ross, who won the prize in 1902 for his discovery of the mosquito transmission of malaria and whose work was carried out in India, no British clinical research worker has yet won a Nobel prize.

In fact, the application of science to clinical medicine within British medical schools and hospitals occurred more slowly than in the United States. By the end of the first decade of the twentieth century, there had emerged a number of outstanding British individuals whose contributions to research in the clinic were internationally recognised. Sir James McKenzie had pioneered the use of the polygraph in the study of the

heartbeat in health and disease. His follower Sir Thomas Lewis had begun his work on the electrocardiogram, invented by the physiologist and Nobel Laureate W. Einthoven in Holland, and he used the new technique for the analysis of the heartbeat and of cardiac arrhythmias. Sir Archibald Garrod of St Bartholomew's Hospital had published his classic volume on *Inborn Errors of Metabolism* and surgeons such as Victor Horsley were making major contributions to neurosurgery and to the understanding of thyroid disease, the use of thyroid extract having been pioneered by Murray in Newcastle in 1891. In addition, Britain's role as a colonial power, particularly in Africa and the Orient, gave opportunities to men such as Sir Patrick Manson, Sir Ronald Ross and Sir David Bruce in the newly developing disciplines of tropical disease. But, as had been the case in the United States, there were at that time no clinical departments, headed by full-time professors, where young men could acquire the training necessary for clinical investigation, as is so clearly illustrated by the young Henry Dale's experience at St Bartholomew's.

Sir William Osler was to be an important figure in Britain at this time. Translated from Johns Hopkins to the Regius Chair of Medicine in the University of Oxford in 1905, he was dismayed by the medical educational desert that he encountered and which he repeatedly criticised in lectures at medical schools throughout the land. The current arrangements were so different to those he had enjoyed in Baltimore.

There were then a number of important developments in Britain that were to encourage the development of effective research in medicine, particularly in the clinic. The first was the *Haldane Report on University Education in London*. Haldane was deeply influenced by German and American experience, and Sir William Osler, who gave evidence in 1911, was a trenchantly critical witness.

When the *Report* was finally published in 1913, Haldane argued strongly for the creation of full-time departments in clinical subjects where the teaching and practice of medicine would be regarded on the same footing as any other department in the pre-clinical or basic sciences. In other words, research would be an integral part of their activities. The move was not universally welcomed by the well-heeled consultants who then controlled medical education in London and the battle between academic and practising consultant was to rumble on for a full half-century. Furthermore, the idea of experimentation in man was deeply suspected. Clinical research on the German model was often criticised, a St Mary's consultant writing to the *British Medical Journal* to complain that the British trained man was often shocked in German clinics by what he thought to be callous handling of the sick.

The year 1913 was also to be the year of foundation of the Medical Research Committee, later the Medical Research Council, and although under its first Secretary, Sir Walter Morley Fletcher, it was to be particularly

orientated to the basic sciences, it also had a major influence on research in the clinic through its support of that brooding genius, Sir Thomas Lewis, at University College Hospital. Lewis championed the cause of what he came to call 'Clinical Science', arguing that it was a subject in its own right which could take its place alongside other disciplines such as physiology or pathology. There were, however, those who argued that by championing the cause of clinical science in this way, Lewis caused a disastrous rift to develop between the clinic and the basic sciences. It is a certain fact of history that Gower Street has proved more of a chasm between science and the clinic than a highway.

Whilst the MRC was often criticised in the 1930s, particularly by the then Presidents of the Royal Colleges of Physicians and Surgeons, Lords Dawson and Moynihan, for its supposed lack of interest in clinical research, it was also taken to task for its support of clinical research, Gowland Hopkins stressing in his Presidential Address to the Royal Society in 1935 that the Council's policy might divert funds that would be more fruitfully devoted to the basic sciences.

There were, however, further important initiatives in postgraduate education that were to become highly influential. The foundation of the Postgraduate School at Hammersmith Hospital in 1935 established a school on the American model that was to be unique in Britain and where research was to be preeminent. As with Haldane's recommendations, the School was for many years criticised in the conservative London undergraduate schools for its commitment to research in the human subject, candidates for posts being warned in other schools that if they went there to work it might irreparably damage their careers. At the same time, the foundation, through the success of the Morris motor car in Oxford, where Osler had so lamented the absence of any medical school, of the Nuffield Chairs in clinical subjects has led through the years to the emergence of the most outstanding school of medicine in Britain today.

There is little doubt that in Britain the basic sciences have been at the forefront of scientific developments in medicine. Sir Henry Dale's work on neurotransmission, the discovery and development of penicillin, the remarkable galaxy of talent brought together by the MRC at its laboratory of Molecular Biology at Cambridge — Crick, Watson, Perutz, Sanger, Klug, Milstein — all Nobel laureates, Sanger twice, and more recently Sir James Black's outstanding work on beta-blockers and the H₂ receptor antagonists are all examples of basic scientific work that has had a major impact on clinical practice. In addition, in applied technology, it was British scientists who pioneered fiberoptics, computerised technology scanning and nuclear magnetic resonance.

For the clinical research worker, success in the modern era has often depended on effective collaboration between basic scientist and academic clinician. British clinical research may appear to the historian to have a

less distinguished tradition than that of the United States as evidenced by the winning of Nobel prizes. It is, furthermore, relatively unusual for a British clinical scientist to be elected to Fellowship of the Royal Society. In fact, British clinical research has a commendable record, particularly in disciplines such as immunology or haematology. The prevention of rH incompatibility by Clarke and his colleagues, the pioneering of hip replacement surgery by a surgeon with an interest in engineering, the effective development of organ transplantation, owing much to Sir Peter Medawar's basic studies of immune tolerance, and more recently the application of molecular biology to human disease by Sir David Weatherall's Institute of Molecular Medicine in Oxford, are all examples of scientific achievements of the highest quality. To these may be added the work of Edwards and Steptoe on *in vitro* fertilisation. These examples illustrate too how important is the creation of the multidisciplinary team, bringing together both clinicians and basic scientists, something which the traditional structure of many existing universities does so much to inhibit because of the rigidity of departmental barriers but at which the MRC has been so much more successful.

The MRC was also involved in two vitally important developments in clinical research in the immediate post-war era. The first of these was the randomised clinical trial. Advised by Sir Austin Bradford Hill, Professor of Medical Statistics and Epidemiology at the London School of Hygiene and Tropical Medicine, the Council set up in 1946 a trial of the efficacy of streptomycin in the treatment of pulmonary tuberculosis. The design followed that adopted by R. A. Fisher in his work *The Design of Experiments* in 1935, when he had recommended that 'randomisation is necessary for the validation of using any test of significance'. The results of the trial were startlingly successful in showing how effective streptomycin was. As the *British Medical Journal* pointed out in its pages in 1948, this was the first randomised controlled trial to be reported in human subjects, and they considered it would serve as a model for other such studies.

The second important development was the application of epidemiology to the analysis of clinical problems, particularly those involved with the frailty of human behaviour. Again it was Sir Austin Bradford Hill who was the key figure. In 1947, stimulated by the Chief Medical Officer at the General Register Office, the MRC had set up a conference to discuss the increased, and increasing, mortality from cancer of the lung. The MRC enlisted the aid of Bradford Hill who was able to recruit the young Richard Doll to undertake the project with him. It was they who showed so clearly the relationship between smoking and cancer of the lung. Their observations were not only important in showing the cause of a commonly occurring cancer in Britain, and subsequently in other countries such as the United States, but also in establishing the position of epidemiology as a discipline in clinical research, at a time when

laboratory scientists and many of those in traditional clinical academic departments, on both sides of the Atlantic, considered subjects such as epidemiology to be 'soft science'. Doll and Bradford Hill's work should surely have been considered as deserving of a Nobel prize as any other scientific achievement cited in this paper.

The evidence of twentieth-century medicine shows clearly how important research, including human experimentation, has been in ensuring that scientific advances have been effectively applied to the ailments of mankind. The prevention of illness by immunisation, the introduction of antibiotics, the discovery of new drugs to treat heart disease, high blood pressure or ulcers of the stomach, and the remarkable advances in surgery that now permit the transplantation of organs as complex as heart, lung or pancreas have all been the result of research based partly in the laboratory, partly in the clinic. There is so much still to do. We know so little about multiple sclerosis, rheumatoid arthritis, mental illness, the cause of premature labour which results in so much neonatal mortality, and many other ailments which kill and cripple mankind. For the future, however, medical research will continue to require the active collaboration of scientists in the laboratory with caring doctors and other health professionals, working to agreed ethical principles at the bedside.

DISCUSSION

SIR CHRISTOPHER BOOTH: I tend to regard art as creative and science as revelatory, in the sense that everything science has done has simply revealed things. Beethoven's Ninth Symphony, on the one hand, could never have appeared without Beethoven's mind and if a bomb had destroyed that symphony in its written manuscript it could never have been recovered whereas scientific discovery, on the other, is not like that. Almost always, if somebody does not discover something, someone else will at a later stage. Again, that is a very black and white view. One argument is that scientists see themselves as creative, but it depends what you mean by creative.

THE CHAIRMAN: I do not want to enter into any discussion on this, but if you had spoken to the sculptor, Henry Moore, he would have said that what he was doing was already contained in the material he was handling and all that he did was to reveal it. However, that is by the way.

SIR CHRISTOPHER BOOTH: I think that is quite true of Henry Moore's sculpture!

THE CHAIRMAN: There are others, too.

DR MICHAEL SWASH: I think Sir Karl Popper might disagree slightly with your last statement, perhaps with the thought that, although science might reveal the truth, the truth itself is subject to change with further scientific endeavour.

SIR CHRISTOPHER BOOTH: I agree with that.

DR SWASH: I found myself recently in a situation, in the United States where we were discussing neurogenic diseases, and there was discussion starting from the MRC trial on tuberculosis. In America and increasingly in Britain, it is becoming very difficult to recruit into trials, because patients say: 'Doctor, you know that the disease is fatal and you know what the time course of the disease is and what the limits are — why do you need to have a control group?' If you try to construct control group studies, the patients go away and find other doctors to obtain the drug without a trial.

SIR CHRISTOPHER BOOTH: Yes, I agree. On your first point there is a lovely story about Sir Thomas Lewis. A South African, Craib, went to have dinner with Lewis preparatory to taking a post with him. Craib picked up a fork and dropped it on the table and said to Lewis: 'Is gravity a fact?' Lewis replied 'Yes.' Craib then said: 'Under those circumstances I cannot work with you for gravity is no more than a theory'.

As regards the on-going debate on the ethics of trials, this is something I do not see as an absolute; it is something that develops all the time. The ethics of medicine are changing with the changing views of society.

MR ALAN MAYNE: In this connection I should like to wear my statistical hat, because I have been a statistician in the past, and I should like to make one or two points about clinical trials.

First, it seems to me that the attitude of the patient to what has happened to him would have some influence on the result by virtue of psychosomatic effects. Therefore, if the patient has been put into a control group with some unease about what has happened to him, would this not to some extent bias the finding of the clinical trial? This is a factor that needs further examination.

Secondly, in 1976 — admittedly as a spare-time activity, as it was not part of my job — I did start a preliminary investigation of the possibility of doing clinical trials, where some statistical evaluation would still be possible, even though patients would be allowed to choose which group to go into. I envisaged this working by taking into account past experiences of different types of treatments, by looking at clinical records of their performance. I showed my draft paper on this approach to several medical researchers but as far as I recall they considered that it had too many difficulties to be pursued at that time. Nevertheless, I view my approach as an interesting possibility worth further enquiry. If anybody

would like to follow it up with me, I still have the records of what I wrote, and could make them available.

SIR CHRISTOPHER BOOTH: That is a very interesting view with which few randomised trialists would be very happy.

As to the extent to which knowledge and being involved in the trial influences results, we do have these very examples of placebo effects. The treatment of peptic ulcers is a very good example of that, where the placebo will achieve a 30 per cent response very effectively. These are the sorts of things where randomisation is crucial to determining these difficulties.

As to whether the mind influences the body, I regard that as still very much unproven. I knew Michael Balint personally and had a great admiration for his work. What he thought about doctors more than anything else was that, when the patient is going out through the door and says: 'Oh, by the way, doctor...', that is the time when you really have to be on your mettle. He thought things like that about the patient interview. I am also proud to have delivered the first Michael Balint memorial lecture last year on the ethics of medicine.

PROFESSOR GEORGE TEELING SMITH: Again on the subject of clinical trials, I think it is worth noting, particularly since my office is supported by the pharmaceutical industry, the fact that following the MRC trial it was on pharmaceuticals that clinical trials were very rapidly and systematically adopted.

I say that in order to bring in the name of Archie Cochrane, because it was not until he published his book on 'Effectiveness and Efficiency' that the medical profession as a whole took on board the fact that clinical trials needed to be applied to surgery and to diagnostic procedures and everything else, as well as simply to pharmaceuticals.

I am sorry that Iain Chalmers, the director of the new Cochrane Centre, is not with us this morning, but I hope that he will be with us this afternoon. I think it is an important development, arising incidentally from an Office of Health Economics meeting thirteen years ago, that the Cochrane Centre, to evaluate clinical trials, has now been established.

PROFESSOR HUGH FREEMAN: Would Sir Christopher like to comment on McKeown's view that scientifically based medicine has made no significant difference to human health until very recent years?

SIR CHRISTOPHER BOOTH: I think Tom McKeown made a very good point. I rather agree with George Godber's assessment of McKeown that he tended to occupy an Olympian position from which he delivered his statements rather like Moses coming down from the top of the mountain. There is obviously truth in what he says, but there is also a lot of hyperbole that takes it too far. There is no question whatever that the science of medicine has got rid of smallpox, not social change. There is no

question whatever that if you want to get rid of cancer of the lung you have to find out scientifically that smoking causes it and then you have to go ahead. Without these scientific developments those things would not happen.

Furthermore, I think one has to remember that a huge amount of social change, particularly in things like housing, to which McKeown referred, were based on scientific developments, particularly clean sewerage, which was based on the bacterial theory of disease. Science lay behind an awful lot of things that were happening.

Although there is truth in what he says, I am sure that increasing longevity in the population is not the result only of medical science; it must be due to many other factors as well.

MR HENRY CONNOR: I started off my career in medicine, but saved humanity a lot of problems and trouble by switching to chemistry and chemical engineering, so I am an outsider. I have heard two magnificent sweeps across the history of science and medicine.

I have a small question which I am conscious may be a red herring. What is the probability of our holding a seminar in the future on the influence of the legal profession on the teaching and, in particular, the practice, of medicine?

SIR CHRISTOPHER BOOTH: I was at a symposium here recently on the impact of molecular medicine on clinical practice, and it was interesting that at the end the American lawyer who was the chairman of the Royal Society of Medicine's American branch in New York told me that he thought they were going to need a whole new breed of lawyers who were molecular biologists to be able to deal with the complexities of the law in that respect. I think that may well be true of a whole range of legal issues coming up now in medicine and in technology which will be very complex and very difficult.

THE CHAIRMAN: Let me end this part of the meeting with a story. When Joseph Needham first went to university he was going to read medicine. His tutor at that time said to him: 'No, no, my boy, you can't do that! Atoms and molecules — that's where the future lies. Atoms and molecules, my boy; you'll have to do chemistry.' So he followed this advice, gave up medicine and contributed greatly to the development of embryology as a researcher and as its historian.

Science and the nervous system

Dr Michael Swash

You will note that my topic is 'Science and the Nervous System' whereas all the other topics have been dignified by clinical names such as 'infection' or 'psychiatry'. I suppose that tells you something about the way in which neurologists have been regarded traditionally as purveyors of science out of clinical work. My topic should really be 'Science and Neurology', I think, to be harmonious with the other subjects. There has been a slight psychological slip of the pen, as it were, in writing down 'the Nervous System' rather than 'Neurology'.

The term 'neurology', as someone has already said today, was first used by Thomas Willis. It is now universal as a term to describe diseases of, and the study of, the nervous system.

Many of us enter neurology because we are interested in the brain and the mind. That is one of the reasons why I entered. It became apparent to me, however, when I was in a training programme in Cleveland, Ohio, run by Joseph M. Foley, that the succession of distinguished neurologists who came to talk to us from across the world almost weekly, were characterised by a difference in subject matter according to age. The older the speaker was, the more likely he was to speak about the brain and the mind, and the younger he was, the more likely to speak about science, so those of us in the back row of the auditorium began to think it was a sign of senescence to talk about the brain and the mind, and that we had better steer clear of that. You will know that many neurologists in recent times have been particularly interested in the peripheral nervous system and muscle, the lowest common denominator of Sherrington's construct of the nervous system, perhaps as a refuge from the difficulties of studying the mind, although I am glad to say that there is now a new British society for the study of neuropsychiatry. This represents a return to the splendid Viennese school that became neglected by Franco-German-British science in the middle of the twentieth century. This fundamental problem of Cartesian dualism remains as the basis for brain research.

The pioneers of neurology studied the basic system — anatomy, physiology, brain behaviour, the motor system *par excellence* — and they looked at the central and peripheral nervous systems as separate entities.

The study of the brain is really all about the motor system, the expression of thought and of action. The motor aspects of brain function are what the brain is for: it serves to integrate internal and external activity, and to express these in motor functions such as speech, as part of communication, or as patterns of behaviour related to locomotion. Most of the brain, therefore, is about movement and motor function; the sensory side is about

the direction of that kind of movement. Part of that sensory function is internalised in relation to thought, and part is externalised in relation to output and action.

The influence of technology has been crucial in understanding brain function and diseases of the brain. In many respects it has determined the ways in which advances have been made. You will see how important this remains.

Much of the early understanding of neurology arose from the study of epilepsy. Willis himself studied it, and Hughlings Jackson, one of my predecessors at The London Hospital, based much of his work on clinical studies of epilepsy, deriving concepts of the lateralisation of the brain function and the localisation of speech and motor, sensory and visual function from the experience of his epileptic patients. Without understanding anything about the neurophysiology of epilepsy in modern terms, he was able to draw accurate deductions as to just how the system worked and construct a hierarchical model of the formation and functioning of the nervous system, based upon his philosophical understanding of Herbert Spencer's writings. This was important in setting out modern notions of how the nervous system worked without getting involved in its structure. He was concerned solely with deriving ideas of how it worked.

Cytoarchitectonics arose largely from the German school of anatomy, and attempted to draw together the strands of specialisation of different aspects of the cerebral cortex, in particular attempting a synthesis of anatomy with physiology in deriving a concept as to how the brain functioned. Sherrington had developed the notion of the brain as a complex web of reflexes, some inborn, some acquired, and tried to produce a more mechanistic approach to understanding brain function. These three strands are coherent in our current understanding of how the nervous system works. We still speak of hierarchies of motor control and of distributive systems of motor control running through the anatomical and physiological structures that we understand as part of that system.

Diseases of the nervous system remain the fundamental brick on which neurologists try to build their understanding of the nervous system.

Much of neuroscience as it currently develops is concerned with adding a superstructure of scientific endeavour to the classification of diseases as understood by neurologists. Unfortunately the cross-talk between the neuroscientists and the neurologists is not as clear-cut nor as fluid as perhaps it should be. The neurologist describes the disease, recognises the clinical features, sometimes understands the pathological appearance, and occasionally these days has also studied the biological and molecular abnormalities in the cell membrane or in the cell itself. The disease is classified in terms of understanding its causation, usually a simple matter of whether it is genetic or acquired or due to infection or a cancer, the

old nineteenth-century classification. Pathogenesis is usually studied serendipitously, but occasionally understanding is achieved by dint of scientific endeavour based upon the pathology or the clinical features. Investigations are then devised to try to understand how best to look after the individual patient and translate the scientific endeavour into clinical practice and treatment, designed, one hopes, scientifically. Most treatments also, of course, have been arrived at serendipitously as a result either of chance observations or intuitive understanding of cross-relationships between different families of compounds or drugs leading to new methods of treatment.

Neurology is still dogged by a number of traditional treatments, none of which is understood and most of which have not been studied: for example, physiotherapy, occupational therapy, psychological treatments for organic disorders themselves and for their social and psychological effects. Much resource is consumed in such treatments and they are all believed in implicitly by patients, particularly, for example, physiotherapy. They are believed in by some clinicians, they are used by all clinicians, but there is no scientific understanding of them, no proof of their efficacy and, if they are effective, no knowledge of when they should be applied, for how long or in what manner. You will all be aware of the other paramedical forms of treatment that are so popular these days — acupuncture, black boxes and other treatments, particularly emotive when applied to retarded children — again totally without a scientific understanding and, more importantly, I think, without an understanding as to whether or not they are effective. If they are effective, then there must be something scientific about them which it is important to study, whereas we tend just to accept that the National Health Service spends millions of pounds on these treatments without knowing whether or not they are of any value.

The common diseases of neurology consist of trauma — the worst of all, really, because it affects young people — tumours, stroke, epilepsy (again, a serious problem for a large number of young people, with about 0.75 per cent of the population affected), multiple sclerosis, the neurodegenerative diseases and, perhaps, some neurotoxin exposures.

The categories of neurological disease that neurologists commonly see include functional disorders — headache and dizziness etc — which I am sure my psychiatric colleague will discuss in relation to psychiatry because such patients are not in fact neurological, in the sense that there is not any neurological disease that one understands as the basis for their problem. However, they come in large numbers to neurologists and consume neurological resources just as they do in respect of psychiatry. Familial diseases are currently of increasing importance because of their putative relationship to neurodegenerative disorders, in many of which there may be a genetic background, a factor that is frightening for the general population and misunderstood by the medical profession.

The minor neurological problems cause much difficulty for neurologists. Headache occupies nearly 20 per cent of clinical neurology consultant time; dizziness is the second most common cause of presentation; minor mental illness is also common, including depression and a multiplicity of symptoms that often require referral to a neurologist simply to provide a comforting reassurance to the other medical attendants that there is nothing organically wrong.

Head injury, as I have indicated, is very important and not well understood in terms of the proper mechanism of management. Great advances have been made recently through the introduction of methods of measuring the rise in intracranial pressure that follows acute head injury, and through CT and MR imaging which demonstrates the shifts in the brain that may occur as a consequence of the injury, and leads to better neurosurgical treatment of haemorrhages that may require evacuation. The brunt of head injury falls on a young age group — those between 15 and 25 years.

The prevention of disability is clearly important. It is not well understood at present because we know little about how to prevent common diseases such as multiple sclerosis and stroke.

Restorative neurology, or neuro-rehabilitation, is another subject beset by dogma and by tradition rather than by understanding of science. Much recent effort has gone into departments of rehabilitation that are concerned with the sociological aspects of the disability — how to care for the patient, how to deal with handicap, how to make the patient feel better, how to reintegrate the patient into the environment, teaching the family how to cope with the disability, how to get the patient back into as normal a lifestyle as possible — but very little effort has gone into finding out how to restore the function of the disabled limbs and impaired sensory function. We know that this can be manipulated pharmacologically and also physiologically. I feel that more effort should be put into understanding the physiology and disturbance of function so that we can better understand how to modify the patient's disability *per se* rather than its secondary consequences, important though this is in caring for the patient's total problem.

How will neurology change? The main lesson is that of neuro-imaging. We live, I suppose, in a post-literate society where television images are very important. In medicine images of the body are important. We are also concerned with trying to achieve a better understanding of physiology, to alleviate more effectively the disabilities I have mentioned, to better utilise biology, to prevent and manage diseases so that we use less invasive surgical techniques, and to improve our understanding of neuropharmacology.

In conclusion, I should like to stress that in a sense neurology was the clinical discipline that initiated neuroscience. It was because the two

went hand in hand that they stayed hand in hand throughout the nineteenth century and the early part of the twentieth. They diverged increasingly as the twentieth century progressed and as neuroscience emerged as a separate discipline, but clinical neurology requires neuroscience in order to continue its development, and it urgently needs to rejoin neuroscience in order to become coterminous with it as part of the common endeavour. If that were to be accomplished, even with our rather limited resources in this small country, I think we could continue to be productive and to lead in some areas of development, as we have managed to do in the past.

There are great opportunities, but I fear that if we are going to accept fixed systems in our training programmes we will lose that flexibility which is so fundamentally important to the training of the clinical neuroscientist and to the way in which he or she works.

DISCUSSION

DR DAVID BUDWORTH: As a physicist, I was taught by people who had worked with Rutherford, and I was brought up to believe that he was rather envious of the better equipment in other laboratories, particularly those across the Atlantic. Therefore I had drilled into me his saying: we have no money, we will have to think. If you really are at the frontiers of something I think it is true that you do not need very advanced equipment, you do not need the absolutely latest thing. It is when people are following up that more elaborate equipment is needed, so maybe that is a consolation to you — or maybe not.

The second point I wanted to make was about the need for contact between science and technology. I regard medicine as a technology, and therefore analogous in policy terms to engineering rather than to science. Quite often, the technology is ahead of the science, and it is important to have a two-way exchange of information and ideas between them.

DR SWASH: I am sure that it is solvable. Currently in the UK there are several small medical schools competing with each other, whereas if there were a few larger ones with a bigger mass they would probably be better.

PROFESSOR JANGU BANATVALA: Many of us are concerned about the long training programmes. The European system has a short training programme. Do you feel that this will be for the good in due course or not? Will it influence our training?

DR SWASH: I think it will, but one must be rather careful. The outcome of some European training programmes is not the same as the outcome of some of ours. The Royal Colleges would rightly say that the

level of experience and the capacity of the trainee in Britain who has been through good training programmes is probably greater than that of the average trainee in some European centres. There is nothing wrong with that. They are producing specialists of a slightly lower, more general, calibre; then they go on, as the Americans do, and train people so they can structure assistant professor grades to become more like consultants in a teaching hospital in Britain. One is looking at the possibility of several different kinds of person coming out of the training programmes.

My concern is to find the trainees who have the capacity and the interest to undertake scientific work early, to give them the opportunity, give them their head, push them forward and take a risk with them and let them develop fast. We have to develop their integrity, standards and clinical skills.

PROFESSOR ROBIN MURRAY: I wonder whether you would accept the view that British neurologists have tended to look for authority not to science but towards distinguished clinicians such as Miller, Brain and Walton. Why does that happen in neurology in particular?

DR SWASH: You are probably right. The names you mentioned and, indeed, the earlier neurologists were leaders in science in their day. Nowadays, the clinician would not be leader in that area because the subject has changed. Neurology simply continued in a clinical mode. However, our exports in neurology, particularly Denny-Brown to Harvard during the Second World War, took the British tradition to America where it developed and changed and was put together with science in such a way that it developed quite differently. In Britain neurological departments remained small, and did not develop academic centrepieces with academic departments, professors and other academic appointments. Thus neurology remained a clinical discipline diffused across the community rather than a centre-based discipline working with scientists to understand the basis of neurological diseases, although there are a few obvious exceptions to this generalisation.

SIR DOUGLAS BLACK: I hesitate to confess this, but I served a sentence as Chairman of the Joint Committee on Higher Medical Training (JCHMT). Whereas the main committee talked of little other than of flexibility, the subordinate Specialist Advisory Committees (SACs) vied with one another in making training detailed and prescriptive — hence the rigidity.

DR SWASH: Yes, I understand.

SIR CHRISTOPHER BOOTH: And I totally agree with that.

DR SWASH: I think the difference again is that in countries where medicine has developed academically the universities themselves have taken hold of the notion that they need to put clinicians in association

with their scientists, and the emphasis has perhaps come from the university rather than from the health care system.

PROFESSOR FREEMAN: Early in your talk I think you were rather dismissive of psychosomatic treatment and passed rather rapidly over it. I am not sure I quite followed your argument.

DR SWASH: I was trying to make the point that these are a form of treatment in which there is a very large resource not only in the NHS but in the private sector, and that the methods used are largely traditional although that is not to say that they are not effective. I was putting in a plea for study of the effectiveness of these techniques and if they are effective, why. I suspect that many of them are not, and that would perhaps be useful information also. It is an emotional study because it is tinged with belief on the part of the general population. With such a large resource, however, I think we should be careful of accepting it without understanding what we are doing; and I do not think that we do understand what we are doing.

DR HOPKINS: I want to thank Dr Swash for a wonderful overview of the place of science in his subject, but I was somewhat surprised that he made no reference to the effects of disordered autonomic nervous system function. As I said in a previous contribution to the discussion, many patients present their doctors with symptoms and actual illnesses which essentially are psychosomatic disorders — I do not think I need to give this audience examples of what these are — but they are generally recognised as being the results of altered autonomic system responses.

After all, there is now a vast literature, mostly written by clinicians over the past sixty years or so, about this. It is many years for example, since Wolf and Wolff reported their experimental work which demonstrated the effect of the emotional state on changes in gastric function. In the same year, Groen recorded his clinical observation that grief often precedes the onset of ulcerative colitis, and Menninger claimed that the skin 'mirrors the emotions better than any other body system'. Yet there seems to have been very little written by neurologists about this. May I ask Dr Swash: is the autonomic nervous system not of any interest to the neurologist, and if not why not?

DR SWASH: Yes, it is increasingly. I take your point. I did not address this aspect of the nervous system. It is perhaps one of the important factors leading to minor neurological symptoms, because they are often of an autonomic nature. For example, because of the interrelationship between the gut and the mind and the fact there are so many neurones in the gut, irritable bowel syndrome is turning out to be an interesting neurological disorder.

SIR CHRISTOPHER BOOTH: I spent a lot of my professional career as head of a big department of medicine teasing the neurologists to the effect that they did not have any diseases they could treat and, if they did have diseases they could treat or prevent, that was because of advances which had come from outside neurology. Comment, please!

DR SWASH: Things have changed!

Science and infection

Professor J. E. Banatvala

Important discoveries which may in due course result in major programmes in preventive medicine, particularly immunisation, often result from epidemiological studies which, in turn, are prompted by astute clinical observations.

One such example relates to the discovery of the Epstein-Barr Virus (EBV). Dennis Burkitt, a surgeon working in Uganda, observed in the 1950s that a lymphoma occurring in the region of the jaws among children appeared to be geographically restricted and often occurred among clusters of patients. The geographical distribution of the tumour occurred in climatic conditions favouring the breeding of mosquitoes. Burkitt put forward the hypothesis that Burkitt Lymphoma (BL) was infectious in origin and transmitted by mosquitoes. In the mid-1960s, Epstein demonstrated the presence of a virus in cell lines propagated from tumours of patients with BL, this virus being a new member of the herpes group of viruses. Although mosquitoes are now known not to be a vector of the virus itself, BL occurs in regions which are holoendemic for malaria, this infection being an important co-factor involved in the pathogenesis of BL.

Seroepidemiological studies showed that EBV is ubiquitous. However, studies in Philadelphia showed that after a laboratory technician developed infectious mononucleosis (IM), her serum which had previously contained no antibodies to EBV, was now positive. Subsequent studies using sera which had been stored from students at Yale University showed that IM occurred only among those who initially had no antibodies to EBV and that following infection students with IM developed an EBV antibody response.

Subsequent seroepidemiological studies showed that EBV is associated with another tumour, this being undifferentiated nasopharyngeal carcinoma (NPC) which is one of the commonest forms of malignant disease occurring in South East Asia. As with BL, it is suggested that co-factors are involved but they have yet to be identified. Recent evidence suggests that EBV may also be involved in the pathogenesis of certain forms of Hodgkin's Disease.

An EB vaccine derived from the membrane of the virus (gp 340/220) has been shown to protect cotton-top marmosets from developing EBV associated tumours. Phase One Trials in humans will shortly be taking place. If successful, further trials to determine whether this vaccine would prevent IM among adults will be carried out, perhaps followed by trials to see whether the vaccine prevents BL and, as a longer term objective, NPC.

There are about 350 million carriers of hepatitis B (HBV) in the world. Most of these carriers are in developing countries, highest carrier rates (10–30 per cent) being detected in sub-Saharan Africa, South East Asia and certain Pacific Islands. Chronic liver disease and primary liver cell cancer (hepatocellular carcinoma — HCC) are common in such parts of the world and seroepidemiological studies have shown that the prevalence of chronic liver disease and HCC closely parallels the distribution of high HBV carrier rates. Most of these carriers are infected perinatally or in infancy. Studies carried out in Taiwan have shown that persons who are persistent HBV carriers are more than x 200 more likely to die from HCC than those who are HBV negative, this connection being considerably greater than that between cigarette smoking and lung cancer.

In order to reduce the burden of chronic liver disease and HCC induced by long-term HBV carrier states, the World Health Organization (WHO) has recommended that countries with carrier rates of >8 per cent should include HBV vaccination as part of the infant immunisation programme by 1995 and that all other countries should follow suit by 1997. Although it is hoped that this programme will be effective, recently some concern has been expressed relating to the emergence of hepatitis B escape mutants, since some infants vaccinated at birth, despite having adequate levels of protective antibody, contracted HBV infection. Among parts of the world where this phenomenon has been observed are included some countries in Europe as well as the Middle and Far East and South America. Molecular biological studies demonstrated that the virus infecting these children was a mutant having an amino acid substitution (glycine to arginine) in an immunodominant region of the hepatitis B surface antigen (the *a* antigen loop), this being the major protective epitope. This change resulted in the vaccine-induced anti-HBs response failing to neutralise the mutant virus. Thus 'molecular epidemiology' has thrown light on a potential threat to the HBV vaccination programme; epidemiologists, molecular biologists and vaccine manufacturers will need to work together in order to assess the significance of hepatitis B variants and, if appropriate, manufacture modified HBV vaccines.

Molecular epidemiology has also been useful in determining the source of an infection involving a number of patients which may have been acquired from a health care worker. This may be illustrated by the case of the HIV positive Florida dentist who infected five patients attending his practice. Part of the hypervariable region of the viral envelope (V3 region of GP120) was sequenced and virtually identical sequences of the proviral DNA were detected in viral isolates from the dentist and five of his patients but not in two other patients or 31 local HIV positive patients not attending the dental practice. Thus, the amino acid 'signature pattern' pointed to five patients being occupationally infected by their dentist.

Although only relatively recently discovered, more is known about HIV than almost any other virus. As might be expected, a considerable amount of activity continues to be directed towards basic science which in turn may hopefully provide the basis for the construction of effective vaccines. More applied research relating to epidemiology and patient management, including specific antiviral chemotherapy, is also an important area of activity.

Despite this research, HIV continues to spread throughout the world and, in the absence of a vaccine or effective chemotherapy which will prolong the duration and quality of life on a long-term basis, health education provides the only weapon currently available for HIV control.

In order to make the most effective use of national and local resources, identifying the prevalence and changes in pattern of HIV infection is of importance in ensuring that resources are targeted accurately. Surveillance of such groups as substance misusers, homosexuals, and patients attending STD clinics are in progress in most developed countries. Assessment of heterosexual transmission may be obtained by carrying out surveillance on women attending antenatal clinics and much of this is being carried out on an anonymised basis. However, in addition to sub-Saharan Africa, HIV is now spreading extremely rapidly in Asia, particularly in the Indian sub-continent and Thailand, infection being spread mainly heterosexually. In such parts of the world, in addition to the groups listed above, it is essential to incorporate such groups as those involved in commercial sex and paid blood donors in surveillance programmes. However, resources are required not only for the purchase of serological tests, all of which have a high degree of sensitivity and specificity, but also for the training of field workers and laboratory personnel to collect and assess HIV prevalence.

During a recent visit to India to advise on HIV surveillance, I was taken around the 'red light' district in Bombay in which the prevalence of HIV has increased from about 2 per cent to 33 per cent between 1987 and 1991; it is estimated that such persons transmit infection to about 6,000 male partners each month. The presence of severe and untreated STDs, which is common among those offering commercial sex in tropical countries, favours the transmission of HIV. On the North East frontier (near the Burmese border), infection occurs predominantly among drug abusers, about 40 per cent having evidence of HIV infection.

The spread of HIV infection in many developing countries is alarming for it is affecting not only the fabric of family life but, since sick young adults are unable to work, it has a potentially disastrous effect on the economy of the country.

During the last decade there has been a dramatic increase in the number of cases of salmonella infection and, since the mid 1980s, this has been almost exclusively due to food-borne infections caused by *salmonella enteritides*. Similar findings have been reported in the USA and

parts of Europe. The annual cost of salmonellosis alone for England and Wales has been estimated to be of the order of £300 million, half of which reflects lost production for sickness absence. The remainder relates to costs to the public sector resulting from health care and local investigation of cases and the effect of sickness on affected individuals and their families. However, salmonellosis is only one cause of food-borne infections and it has been estimated that the overall cost of food-borne infections approaches a billion pounds per annum.

Although health education directed towards those involved in food preparation, including housewives, may reduce the burden of infection, the radiation of poultry would provide a cost effective and safe method of obviating much of the risk of food-borne infections acquired via poultry. However, it has so far been difficult to persuade British housewives of the safety of this procedure.

Surveillance studies carried out in hospitals have shown that about 20 per cent of patients are infected on any one day, about half being the result of infections acquired in hospital. In addition to the morbidity and mortality induced by such infections, which include multiply resistant *staphylococcus aureus*, such infections cost somewhere of the order of about £120 million per annum. Infection control teams are of major importance in this context and, if given appropriate training and support, should be able to save many times more than the resources required for their funding.

Tuberculosis is once again beginning to re-emerge as a major threat to the public health. This partly reflects homelessness and poverty as well as the deteriorating infrastructure for populations living in deprived inner urban areas. However, a markedly increased incidence of infection has been noted in such parts of the USA as New York City and this correlates largely with the rising incidence of HIV infections. In such areas, old sanatoria have been reopened and new ones constructed. The problem is compounded by the finding that about one third of patients have organisms resistant to chemotherapy and that patients undergoing successful treatment may be superinfected with resistant strains.

Studies are now in progress in Britain in order to determine whether notifications for tuberculosis link with HIV positivity.

Vaccination is probably one of the most cost effective measures of reducing the morbidity and mortality from infectious diseases.

In Britain immunisation uptake in infancy and childhood has improved markedly during the last five years. Thus, uptake rates are now of the order of about 90 per cent in many regions although there are a few districts, particularly in deprived urban areas, where there is still room for improvement. Following the augmentation of the rubella vaccination programme in 1988, which involved giving the combined mumps, measles and rubella (MMR) vaccine to pre-school children,

notifications for these infections have declined and been sustained at very low levels. 1990 was the first year in which no measles-related deaths were reported. Although some cases of measles continue to be reported, particularly in small infants, recent studies carried out by the Public Health Laboratory Service have shown that clinical diagnoses are usually inaccurate. Thus, infection was confirmed virologically in only about 5 per cent of children aged less than four and 18 per cent of those aged five to nine.

It is encouraging that two new vaccines have been licensed this year — hepatitis A and *Haemophilus influenzae type B* (Hib).

Hepatitis A virus (HAV) is an inactivated virus prepared by a method analogous to inactivated polio vaccines. Although HAV was discovered in the early 1970s, poor yields of virus in cell culture delayed preparation of this vaccine until recently; it is fortunate that small concentrations of inactivated virus are highly immunogenic. Notifications of HAV infection, which are now of the order of about 7,000 p.a., have increased markedly in Britain in recent years. Although this is in part due to increased awareness and availability for laboratory diagnosis, there is little doubt that there has been a real increase in the incidence of infection. 20–25 per cent of infections are acquired as a result of travel or residing in HA endemic areas, which include developing countries in many tropical areas as well as parts of Southern Europe and the Eastern Mediterranean. More than 30 million travellers from industrialised countries visit HAV endemic areas annually and about 1.6 million are from Britain (~600,000 for the first time). In 1990, 560,000–600,000 doses of human normal immunoglobulin (HNIG) were given to protect British travellers from acquiring HAV infections abroad. Infections acquired in Britain may result from food-borne outbreaks, particularly the consumption of sewage-contaminated shellfish. However, HAV infections have now become endemic in some deprived urban areas, the prevalence of infection persisting in such communities for periods which extend well over a year.

The vaccine, which is well-tolerated, induces a good immune response in virtually 100 per cent of vaccinees after two doses two to four weeks apart; a third dose at six or twelve months will boost antibody levels and hopefully provide long-term immunity.

This vaccine, which induces antibody levels considerably in excess of those induced by HNIG, should be given to those travelling to HAV endemic areas, particularly if they are going to reside there for a period which is greater than the relatively short-term protection induced by HNIG. Those exposed occupationally, for example sewerage workers, should also be vaccinated and consideration should also be given to vaccinating haemophiliacs since it has recently been shown that Factor VIII concentrates may be HAV-contaminated. Until it is known whether vaccination reduces the amount of virus excreted, it is premature to

include food handlers as a group requiring vaccination. Hopefully, studies will shortly be conducted to determine whether vaccination is effective in interrupting HAV transmission in community outbreaks.

Hib is a major cause of severe meningitis as well as epiglottitis and septicaemia in children. Those who recover from meningitis may be left with residual sequelae including deafness, fits and intellectual impairment. Studies in Oxford and in Wales estimated that the incidence of invasive Hib infection was of the order of 3.4 per thousand children under the age of five (1 in 600 children therefore develop the disease before their fifth birthday). Furthermore, it appears that the incidence of infection in Britain has increased in recent years.

Although Hib vaccines containing purified capsular polysaccharide were made in the 1970s, they were unfortunately non-immunogenic in children aged less than eighteen months and it is in this age group that infections are severe and are associated with high mortality rates. Recently vaccines in which the capsular polysaccharides have been conjugated with various bacterial capsular antigens have been developed and these have been shown to be immunogenic in young infants. This vaccine has now been incorporated into the routine immunisation schedule for infants.

Considerable adverse media publicity, which affected public confidence, was generated in the early 1970s resulting from reports which stated that whooping cough (pertussis) vaccine caused brain damage. Although subsequent studies showed that the evidence linking pertussis vaccination with brain damage was extremely flimsy, the uptake of pertussis vaccination in infancy had declined from 80 per cent in 1973 to about 30 per cent two years later. Between 1977 and 1979 over 100,000 cases of pertussis were reported and a further epidemic occurred between 1981 and 1983. Fortunately the uptake of pertussis vaccination is now of the order of 85-90 per cent and in 1991 only 5,200 cases of pertussis were notified. However, the adverse publicity in the 1970s and early 1980s had a 'ripple effect' on the uptake of other vaccines in infancy and childhood.

In 1992 there was considerable adverse publicity relating to the mumps component of MMR vaccine. Although it was known that the mumps strain (Urabe) used in the MMR vaccine distributed in the UK was more reactogenic than the strain incorporated in the vaccine used in the USA (Jeryl Lyn), the Urabe strain was selected since it was thought to be more immunogenic. Studies carried out following the introduction of MMR in the UK suggested that the mumps component of the MMR vaccine induced a mild aseptic meningitis in only 1:250,000-1:400,000 vaccine recipients. However, further studies produced evidence suggesting that the incidence of aseptic meningitis was much higher, being of the order of between 1:4,000-1:11,000. Serological studies carried out at

about that time showed that, although immune response induced by the Urabe strain appeared superior by an enzyme immunoassay, by neutralisation there were no significant differences. Since virus neutralisation correlates with protection and as the Jeryl Lyn strain does not appear to induce aseptic meningitis, the MMR vaccine containing the Urabe strain was withdrawn and one containing the Jeryl Lyn substituted. Once again, needless anxiety was created by the media who, despite being provided with accurate information of a non-alarmist nature by a number of experts, chose not to publish a responsible account of the situation, overdramatising the risks and severity of mumps vaccine-induced aseptic meningitis, and not mentioning the real benefits induced by MMR vaccine. Some newspapers even went as far as tilting at the well-recognised benefits of measles vaccination. In France, it was decided not to withdraw the vaccine incorporating the Urabe strain.

Since mumps is a common infection, it was of importance in assessing the frequency and severity of vaccine-induced CNS complications to distinguish between naturally acquired and vaccine-induced infection. Fortunately molecular biological techniques employing gene amplification (polymerase chain reaction) made it possible to distinguish between vaccine and naturally-occurring mumps virus in the CSF. Thus, nucleotide sequencing of an amplified region of the gene coding for the fusion protein showed consistent differences between naturally acquired and Urabe virus strains. It was also shown that differences could be detected between the Jeryl Lyn and Urabe vaccine strains.

In 1977 less than 5 per cent of the world's children were adequately immunised against such killer diseases as diphtheria, pertussis, tetanus, tuberculosis, measles and polio. Indeed, acute diarrhoeal disease and measles still represent the two major causes of mortality in children under the age of two in developing countries. As a result of the WHO's expanded programme on immunisation (EPI), by 1993 it is estimated that immunisation uptake rates in many developing countries now approach 70 per cent for DPT, BCG, measles and polio and, by the year 2000, it is hoped that 90 per cent of children will have been immunised.

By 1992, the WHO EPI estimated that immunisation had prevented 1,651,000 deaths from measles, 445,000 from tetanus, 515,000 from pertussis, and prevented 409,000 cases of paralytic poliomyelitis.

Although these figures are encouraging, immunisation rates in certain countries or regions within them are still poor. Effective vaccination programmes are dependent on such factors as preservation of the 'cold chain' from manufacturer to vaccinee, training for those involved in immunisation and surveillance, and freedom from natural disasters and political upheaval. In this context, it is relevant that outbreaks of infectious diseases preventable by immunisation are now occurring in parts of Eastern and Central Europe which hitherto had high immunisation uptake rates.

Recently advances in technology, particularly the application of DNA technology to the development of vaccines, have made it possible to construct new vaccines against a number of infections for which there are already existing vaccines as well as those which have hitherto not had vaccines developed against them. The WHO is now pursuing a new initiative (Childrens Vaccination Initiative — CVI) in an attempt to co-ordinate and harness technology to provide an effective immunisation campaign involving multiple antigens. An ideal composite vaccine should be given at birth as a single dose and preferably by mouth. Perhaps a 'piggy-back' vaccine using a single carrier could be used. Employing micro capsules, slow and sustained release providing long-term protection might be achievable. However, to be successful, such a vaccine must also be heat-stable, well-tolerated and, of course, cheap.

The strategy for the development of such vaccines is dependent on having a clear understanding of the immune mechanisms involved in protection which, in part, requires identification of the microbial epitopes which induce protective immunity (not only humoral but also cell mediated). Having identified such epitopes, they will need to be expressed in suitable vectors. Thus, by recombinant techniques, it is possible to insert the appropriate sequences of DNA into such vectors as vaccinia, Canary Pox, adenoviruses, BCG, yeast, non-virulent *Salmonella* sp or *E. coli*. This construct may then be tested for immunogenicity and efficacy in animal models, which may also be used to determine the optimal route of inoculation, prior to commencing Phase One trials in human volunteers.

Progress towards recombinant vaccines is relatively slow although a number of microbial proteins has been expressed and found to be immunogenic. These include herpes simplex, human papillomavirus 16, Japanese Encephalitis, Lassa Fever, measles, Yellow Fever, HIV-1 and rabies. However, as yet, only hepatitis B, which is expressed in yeast, is licensed for use; it remains to be determined whether some of those listed above and others undergoing trial experimentally will be successful in humans.

Although the goal of the WHO's CVI is unlikely to be realised for a considerable time, the concerted efforts of epidemiologists, microbiologists and molecular biologists now make it potentially possible to provide the most cost effective method for reducing and eventually eradicating infections which kill and maim, perhaps the greatest challenge currently facing the world being HIV. However, in order to achieve this goal, it is essential that adequate resources are directed towards a multidisciplinary approach for research into prevention of infection.

DISCUSSION

DR JEFF KIPLING: Is it not a case of educating the regulatory bodies of the implications of their actions for public confidence in science and medicine when medicinal products such as the vaccine are withdrawn at very short notice without a full explanation of the reasons?

PROFESSOR BANATVALA: No, I do not think you can blame the public themselves since they are readily led, in areas in which they have no expertise, by the media. I have already given you my views on the unnecessary furore which accompanied the withdrawal of the MMR vaccine containing the Urabe strain even though the meningitis it occasionally induced was mild. One of the problems is ensuring that a central organisation like the Department of Health can reach general practitioners and pharmacists as quickly as possible, at least before the media pick up 'straws in the wind' which they wish to misinterpret in order to sell newspapers. Unfortunately, general practitioners and pharmacists do not all have faxes or on-line computers; when they do, it will be easier to disseminate important information.

DR KIPLING: I understand that the French authorities did not withdraw the vaccine.

PROFESSOR BANATVALA: No, the French do not suffer quite so much from the sensationalist publicity accompanying so-called adverse reactions to vaccines. This seems to be a particularly British preoccupation.

THE CHAIRMAN: I should like to make a comment following what Jeff Kipling has said. I feel very strongly that it would be almost impossible to get any real understanding through traditional methods in the popularisation of science, if I may use the phrase. We really need something quite different. We need a flexibility of approach that is immediate and does not take X years to get through. We also need a quite different public relations effort. I do not want to spend any time on this.

With regard to HIV, it is quite obvious there are other centres round the world in a similar position to Bombay.

PROFESSOR BANATVALA: Yes, I am afraid there are. I visited nine centres in India, all of which had shown a substantial increase in HIV although not, as yet, very much AIDS. Most of the infection is heterosexually acquired but, as I said, drug abuse is the major route of transmission in the states near the Burmese border. Unfortunately, some professional blood donors are involved in drug abuse and visit prostitutes. You probably read about the enormous increase in HIV in Thailand as well as in Brazil.

Although it is all we have, how effective is education? After I had given a talk on HIV prevention at a medical school in India, the dean told me

that he had an active programme in educating his students about HIV. I asked him whether his students had access to condoms. He said 'Ssh! We are standing just outside the girls' hostel.'

SIR CHRISTOPHER BOOTH: The point you made about irradiated food is a very important one. What I think was wrong was the introduction of this on scientific grounds without any real public education at all. We are now moving into a new situation with genetically engineered food; for example, tomatoes with this anti-softness nonsense gene being inserted, and so on. ICI are doing this. A trial is being done with volunteers taking the food, doing randomised trials, seeing whether people can tell the difference between one tomato and the next because a lot of people are saying: 'Those are mucked-about tomatoes: they are not right: I am not going to eat them.' People said exactly the same about irradiated food. Something has got to be done, particularly in the food area to get a better system of transfer into popular thinking.

PROFESSOR BANATVALA: There were a number of misconceptions about pasteurisation in the very early days. People were convinced it altered the nutritional state and the taste of milk; as we know, neither is true. I do not know whether there is a science for educating the public. We will hear about that this afternoon.

THE CHAIRMAN: I can tell you immediately — I will do a bit of self-advertisement — that there is a book of mine called *The Science Critic*. You can get it from your local library. Do try and read it, because it deals with this problem in some detail.

PROFESSOR BANATVALA: Public education is such an expensive business. Current arrangements in the EC are such that different foodstuffs from different countries with different standards of hygiene cross national borders regularly. Bavarian salami sticks contaminated with salmonella were introduced into many countries, including Britain. Fortunately, surveillance carried out by the Public Health Laboratory Service ensured that this problem was identified and dealt with fairly rapidly.

THE CHAIRMAN: There is a kind of media fundamentalism, it seems to me, concerned not with the transmission of real knowledge but with the transmission of sales knowledge, and this, as I call it, media fundamentalism is reflected in the religious fundamentalism that is now destroying — I hope not — or affecting the Indian subcontinent. There is this fundamentalist approach which is disastrous these days. If we want to educate, I think we have to look at fundamentalism.

MR CONNOR: One of the problems we have is that what is transmitted, more and more, is not facts but perceptions. One of the most pernicious perceptions that we have today is the zero-risk society, as Sir

Solly Zuckermann once called it — total safety. Endlessly our media interview personalities on television and ask questions like: ‘Can you guarantee total safety? Are you satisfied that this is absolutely safe?’, whatever it is, a vaccine or anything else. There is no perception that almost everything contains a risk, a probability of something adverse happening. That is an education issue, if anything is.

PROFESSOR BANATVALA: I am sure you are right. Although I rather defended the mumps vaccine issue, I think our surveillance might initially have been of a more intense nature, for introducing a new live vaccine relying on the yellow card system as well as requests to paediatricians to report cases was insufficient. Had we been more aggressive and said ‘We are going to examine the CSF from every child admitted to hospital with a possible CNS infection’, we might have obtained a more accurate assessment of the risks of a complication, albeit a minor one, rather sooner.

SIR CHRISTOPHER BOOTH: If I may take up the point about zero risk, the best publication on this is the BMA book *Living with Risk*. Sir Douglas Black chaired the committee that produced it. It went over the whole question of risk assessment in a wide range of areas. I think it is quite the best publication that ever came out on the subject.

THE CHAIRMAN: There was a Royal Society study on the whole question of risk run by Sir Frederick Warner.*

THE CHAIRMAN: That was so pleasant a lunch, and so delightful my luncheon companions, that we are a little late in beginning. We are now concerned with the third of what I call the case studies, and this is on science and psychiatry, to be given by Robin Murray, Professor of Psychological Medicine at King’s College Hospital and the Institute of Psychiatry. He graduated from Glasgow in 1968 and after completing his medical registrarship switched to psychiatry, and came to the Maudsley in 1972, where he has been ever since apart from a period of one year at the National Institute for Mental Health. Until 1989 — that is, for seven years — he was Dean of the Institute of Psychiatry and since then has been head of the joint department of Psychological Medicine between the Institute and King’s College Hospital. So I have great pleasure in asking Robin Murray to speak on science and psychiatry.

*The report, *Risk: Analysis, Perception and Management*, is available from the Publications Sales Department, Royal Society, £15.50

Science and psychiatry

Professor Robin M. Murray

There has been a clear plot to the papers given so far. We have seen the 'good guys', in the shape of the scientific clinicians, vanquishing the reactionaries in several different fields of medicine. However, the story is more complicated in psychiatry, first of all because the battleground is still in dispute and secondly because the scientists are not necessarily always the 'good guys'. Indeed, treatments introduced in the name of science have, at times, inflicted considerable damage on psychiatric patients.

The origins of modern psychiatry, like the origins of academic medicine, lie in Germany at the end of the nineteenth century, and in particular in the schools developed by Emil Kraepelin on the one hand and Sigmund Freud on the other. Kraepelin introduced to psychiatry the model which was being applied to many medical diseases at the time: he believed that one could distinguish psychiatric conditions on the basis of their phenomenology and course; that one should study the incidence in different populations and search for a biological substrate. This model soon proved very appropriate in certain fields of psychiatry. For example, Alzheimer was one of the members of Kraepelin's department and, of course, described the neuropathology of the disease that now bears his name.

The Kraepelinian disease model was the dominant influence on psychiatry until the 1920s when it became apparent that there was a limited application of neuropathology and genetics to many of the maladaptive behaviours which confronted psychiatrists; clinicians found that their knowledge of the neuropathology of organic disorders, such as Alzheimer's disease, did not help them in their management of neurotic patients. Then several leading members of Kraepelin's school became involved in the Nazi eugenic movement and with legislation concerning the sterilisation of the mentally handicapped and the mentally ill. The compromises that such individuals made with the Nazis, brought into disrepute the disease model which was so identified with Kraepelin's school. Indeed, by the 1950s, the idea that medicine had any relevance to mental illness was much disputed, and psychiatry appeared to be leaving medicine for social science.

With the emergence of effective psychotropic drugs in the 1950s, the pendulum began to swing the other way. Many patients who had been psychotic and in mental hospitals for many years were found to benefit from anti-psychotic drugs or antidepressants; it was obvious that the direct effect of such drugs on the brain must have something to do with their improvement.

In order to study the effects of psychotropic drugs on a particular condition, it was necessary to be able to reliably identify patients with the

condition. Yet it soon became apparent that when a clinician in Australia reported the treatment of a series of patients suffering from 'anxiety disorder', he might be studying patients who were substantially different from those that a psychiatrist in Britain would regard as suffering from 'anxiety disorder'. Consequently, throughout the '70s there was a great deal of interest in the question of whether psychiatric conditions could be defined in such a way that investigators could carry out research in different countries and know that they were dealing with the same disorder. Operational definitions of different illnesses were developed, and now have a high level of reliability.

In the 1980s neuroscience and brain imaging began to have a major impact on psychiatry. Psychiatry began increasingly to overlap with neurology and with the topics on which Dr Swash spoke this morning. We are now in what might be called a neo-Kraepelinian phase, in which the biologists have been taking the lead in psychiatric research.

Throughout this century, and particularly influential in the middle years, there has existed an alternative way of looking at psychiatric disorders, the psychoanalytical model, again with its origins in the German-speaking world. Freud's views did not have wide influence until after the First World War, but then became increasingly popular in the United States. Many psychoanalysts were Jewish, liberal or left wing, and consequently they were very much at risk in the years of Hitler's domination in Germany. A number emigrated to the United States and discovered that the psychoanalytical model and the free-enterprise ethic were symbiotic. For example, Pulver argued that 'Freud was fully aware of the potential dangers of extremely low fee or gratuitous analysis'. Both psychoanalysis and American capitalism were highly individualistic and both were concerned with self-improvement.

If one looks back to the peak of the psychoanalytical supremacy in the 1950s, one sees that American psychiatrists claimed that what could be learnt from the study of psychoanalytical doctrines could be applied not just to psychiatry but to architecture and to town planning, to the way one should bring up one's children, to issues of poverty, of feminism, of race, and of war and peace. This attitude was typified by the statement of Kubie that 'all cultural influences and institutions must become infused with knowledge that can be gained only from the study of the lessons of illness'; by that he meant the interaction between the analyst and his patient. Such over-reaching ambitions formed the basis for the rise of the media psychiatrist whom Miller accused of misusing his jargon 'to confuse every topical issue in an incessant series of television interviews'.

However, from the 1950s onwards behaviourists like Hans Eysenck had been pointing out that there was no evidence that psychoanalysis, even when prolonged, actually benefited patients, and gradually there was a loss of belief in the intellectual tenets underpinning psychoanalysis.

There was a period of renewed faith during the 1960s when R. D. Laing re-synthesised psychoanalytical and Marxist ideas and developed the concept that many psychiatric disorders were consequent upon capitalist society or pressure from the nuclear family. But the last thirty years have seen a progressive decline in the influence of psychoanalysis.

There are considerable similarities between psychoanalysis and religion, and not only in their common attempts to explain the inexplicable. Freud became regarded as a prophet, and Freud, of course, identified with Moses himself. Furthermore, Freud had various disciples such as Jung and Adler who engaged in ferocious disputes; there were schisms between the fundamentalists who wished to stick to Freud's original texts and the revisionists who kept updating the doctrines. Many observers commented on the similarity between analytical training and religious indoctrination. The trainee analyst has to spend an hour a day with his or her analyst for three years. Having invested that amount of time and money in psychoanalysis, he or she may find it rather difficult to look objectively at the truth or otherwise of the tenets of the faith.

Analytical ideas are very difficult to test, and to test the effect of psychotherapy you have first to make sure that the therapist whose patients you are studying is a competent one. Psychotherapists are not standard in the way that penicillin is, and this immediately creates a difficulty. As noted above, there is also the question as to whether those interested in psychoanalysis welcome the testing of their approach. Arthur pointed out that there has been a feeling, 'often anti-intellectual in tone, that the process of enumeration, categorisation and statistical analysis cannot reflect the complexity of human interaction between those who help and those who are being helped'. Can personality and interpersonal relations be reduced to the sort of numerical data which are necessary for research? Many analytically-oriented psychotherapists contend that they cannot.

Although the influence of psychoanalysis within psychiatry has declined, there remains a tremendous demand for counselling and for help with interpersonal problems. The Kraepelinian model has little to offer people who have genuine suffering in their daily lives and in their interpersonal relationships. The therapy market abhors a vacuum and as analysis declined so alternative therapies, few of which were science-based, proliferated. As I have noted elsewhere: 'Primal scream therapy, transactional analysis, biosynthesis, Gestalt, family and network therapy compete with cults based on Eastern philosophies and a bewildering variety of encounter and sensitivity groups.'

Fortunately, the last thirty years has also seen a more sophisticated development in the emergence of behavioural and cognitive models. For example, behavioural therapy, based on learning theory, addresses the phobia or obsession in the here and now rather than attempting to trace

it back to childhood experiences. Increasingly, too, the social psychiatrist and the epidemiologist have begun considering the influence of society, the effects of wealth, poverty and unemployment, and a person's role in society, on psychiatric disorders.

It used to be said that if you consulted a psychiatrist it did not matter what you suffered from, but which kind of psychiatrist you chose. If you went to a behaviour therapist, no matter what was wrong with you, you would have behaviour therapy; if you went to a biological psychiatrist, no matter what was wrong with you, you would have drugs or ECT. Psychiatrists now are much more eclectic, but there is still a difference in that the proponents of the behavioural, social and biological models would regard themselves as science-based, but most psychoanalysts would no longer do so.

It is not just the anti-scientists who have harmed psychiatric patients; science has frequently over-reached itself in psychiatry. Psychiatrists tend to follow medical fashion, and in the early years of the century an influential American psychiatrist, Henry Cotton, developed the idea that much mental illness was consequent upon hidden infection. This 'focal infection' theory of insanity was introduced in the name of scientific progress, and as a result there was a vogue for taking out all the teeth of chronically psychotic patients; when this did not work, it did not mean that the infection theory was wrong; it just meant that the infection was somewhere deeper. This led to harrowing operations, such as the removal of sections of the colon because it was known that there were bacteria lurking in the colon. Sadly, their removal did nothing to improve the patient's mental state and gradually this bizarre therapeutic infatuation faded.

Unfortunately, even more patients were put at risk in the 1940s and 1950s when neurosurgeons became attracted to the idea that leucotomy was an effective treatment for schizophrenia. Subsequently that too was discredited, and we now know that the psychological deficits with which many people were left, were much more serious than their original illness.

There has recently been a curious development in that drug companies have created psychiatric conditions. One company, for example, effectively bought the American psychiatric establishment by pouring huge sums of money into academic departments in order to study a particular form of anxiety which they called 'panic disorder', and for which they proposed a particular benzodiazepine as a specific treatment.

The creation of 'panic disorder' was just one example of the 'psychiatrisation' of everyday life. To what extent should psychiatry intrude into our daily behaviour and make syndromes out of normal reactions? In the United States, there is great financial pressure on psychiatrists to find more people on whom to practise their profession. Thus, distressing experiences and their aftermath have been transformed into post-traumatic

stress disorders, difficulty in falling asleep is now 'primary insomnia', jet lag is now a symptom of 'time-zone syndrome', while imagined ugliness is 'body dysmorphic disorder'; slight unhappiness has become 'dysphoric disorder', and the feeling of let-down that follows a holiday is legitimised as 'post-vacation dysphoria'.

Which aspects of behaviour can we reasonably expect science to explain? We certainly cannot explain many aspects of the interpersonal problems which arise in people's lives in terms of our present-day knowledge. In the future, we may hope to explain such complex systems in terms of science but at present, expansionist psychiatry is going far beyond the bounds of what it is qualified to do.

These are some of the problems which face psychiatry. Let me offset them by briefly discussing schizophrenia, where there has been considerable progress, and patients have been greatly helped by the advance of science into psychiatry.

Throughout the nineteenth century, psychotic patients accumulated in mental hospitals. There was a steady increase until the introduction of the antipsychotics in the 1950s; then a progressive fall. The antipsychotics have brought great benefits, and we are now in a situation where new, and better, antipsychotics such as clozapine are being developed, and increasing numbers of people who have been in mental hospitals for many years are beginning to return to the community.

There has been great difficulty in defining schizophrenia. In Camberwell, for instance, where I work, between 1965 and 1984, 470 individuals were diagnosed schizophrenic by their psychiatrists. However, we now have various operational definitions whereby a patient may have schizophrenia if he has A, B and C, but not X, Y and Z. According to the Research Diagnostic Criteria there were 321 schizophrenics in Camberwell; with DSM III-R criteria there were 196 schizophrenics; while Feighner's criteria defined 135 people as schizophrenics.

I have likened this to the situation regarding hamburgers. A McDonald's hamburger is a highly reliable hamburger; in Los Angeles or Moscow or London it is always exactly the same. I suggest that the kappa coefficient of a McDonald's hamburger is at least .96 — that is, they are all exactly the same. However, McDonald's hamburgers are slightly different from Burger King hamburgers, and these in turn differ from Wendy's hamburgers. These different hamburgers are all highly reliable but have any of them any validity? What do the burgers consist of? Is there any meat in them, or are they entirely soya bean?

That is the question with schizophrenia. Are these operational definitions simply artificial constructs without any biological meaning or do they contain an entity? Schizophrenia is a syndrome, but is there within it a particular disease in which there is something biologically wrong with the brain? We now know that this is so!

We know, for example, that there is a genetic predisposition to schizophrenia. Where an identical twin has schizophrenia, in about half the cases the second identical twin also has schizophrenia; but in the remaining cases the second twin will not be schizophrenic. This provides us a wonderful opportunity to compare the schizophrenic with his well identical twin as a control. So we and others have examined the brain scans of schizophrenics and their identical co-twins on CT and MRI scan. The schizophrenic twin almost invariably has larger cerebral ventricles and smaller temporal lobes than his normal co-twin. Presumably some environmental catastrophe has affected the developing brain of the schizophrenic to cause brain dystrophy and compensatory ventricular enlargement.

These are static brain lesions which seem to be present from the time of birth or even before it. Neuropathological investigations have revealed cytoarchitectural abnormalities in the hippocampi and hippocampal gyri of such a kind that it seems they can only be a result of a developmental abnormality. They seem to arise about the fifth month of pregnancy at the time the cells in the ventricular zone migrate to their normal position in the hippocampal gyri. But in schizophrenia the cells do not reach the normal position; they come to rest in positions which are too deep,

A curious thing about schizophrenia is why it does not die out. In 1964 Julian Huxley and his colleagues stated: 'The fertility (reproductive fitness) of schizophrenics is only about 70 per cent of that found in socio-economically comparable normals. The incidence of the disease would therefore be rapidly reduced to the level where it is maintained by mutation alone, unless its selective disadvantage of lower viability and fertility were compensated by selective advantage.'

Why, given that individuals carrying the gene for schizophrenia are less likely to reproduce, does schizophrenia not die out, unless there is some compensatory advantage? Huxley and colleagues suggested that perhaps the reason was that the predisposing gene also conferred resistance to some infections.

This has become particularly relevant in the last few years because of the evidence that schizophrenics have an unusual seasonality of birth. English data show that schizophrenics are 20 per cent more likely to be born in the spring than in the autumn, and it has been suggested that this is because they are *in utero* during the cold winter months when mothers are particularly likely to be exposed to viral infections.

In Finland, following the Asian 'flu epidemic in October 1957, there was a doubling in the number of people born in the spring of 1958 who went on to develop schizophrenia. We carried out a replication study in England and Wales relating to the birth dates of some 14,000 schizophrenics. Again, we found that Asian 'flu was followed by an almost doubling of the number of individuals born who went on to develop

schizophrenia. There are now seven studies which have shown that being *in utero* about the fifth or sixth month of pregnancy during a 'flu epidemic increases the risk of going on to develop schizophrenia. There have been two negative studies, but there is also additional evidence from other influenza epidemics that prenatal exposure increases the risk of schizophrenia. This fits in neatly with Huxley's idea. If an individual carries a gene which is involved in resistance to viral infection, then this will be an advantage most of their life, but if a woman carrying such a gene is infected in the mid trimester of pregnancy perhaps the immune reaction to the viral infection may be disadvantageous to her unborn child. Perhaps the maternal antibodies establish some autoimmune reaction which damages the brain of the developing foetus and increases the risk of later schizophrenia.

Within the conditions seen by psychiatrists, there are disorders such as Alzheimer's disease and schizophrenia which have many similarities with traditional medical disorders and where the application of the usual scientific models is relatively straightforward. We are now beginning to make considerable advances in such disorders. However, there are many other areas of psychiatry where science has yet to make much of an impact, and where fashion and folk psychology continue to hold sway. As Birley noted: 'The field of psychiatry is at present littered with a mixture of irrefutable theories which explain a great deal, and refutable theories which explain only a very little.' Psychiatry remains a huge challenge to science.

DISCUSSION

PROFESSOR FREEMAN: You said, Robin, I think, that Freudianism was in decline, which perhaps in the scientific sense is true, but I think the intellectual interest in it is greater than ever. The number of books and publications coming out shows no sign of slackening off, and it seems to be beginning to grab the attention of people from a wide variety of disciplines.

PROFESSOR MURRAY: I agree with that, but if you were to look crudely at the numbers of chairmen of departments of psychiatry in Britain and the United States who were analytically orientated, it would now be very small. But as orthodox psychiatry has lost interest in Freud, the literary world and the philosophical world have taken him up with great enthusiasm.

DR SWASH: But the interest in Freud in contemporary writing is not entirely in relation to psychosis. It is in relation to depressive illness and to social problems and the problems of adaptation in society, education and artistic interpretation.

PROFESSOR MURRAY: Yes. There is of course a furious debate, and two weeks ago we had a visit from Fuller Torry, one of the American opponents of Freud, who has just published a book called *The Freudian Fraud*, on the malignant effect of Freudian theory on American culture. His contention is that much of modern American thought is influenced, he would claim in an adverse way, by Freud. The difficulty with such an argument is that it is rather like saying: 'Are you for or against Darwin?' The geneticists and evolutionists have moved on, but we continually argue whether everything that Freud said was true or everything that Freud said was wrong. Presumably one should look at him in his historical context.

DR HOPKINS: It seems to me that the contents of the book quoted may be saying much more about its author, than about Freud. There is an ever increasing number of well-written books and papers about the good effects of psychotherapy — not necessarily analysis. You talked about Freud and the Nazis, and how this later affected the decline of Freudianism, but his work is still widely quoted and his methods used in this country as well as elsewhere, so I do not think you should generalise about this.

Again, I am not happy about your lumping together the same approach to the neuroses and to the psychoses. They are two very different groups of illnesses. Your X-ray of a schizophrenic man showing the enlarged ventricles of his brain does not account for the schizophrenics who improve, and even appear to recover. I once had as a patient a well-known professor of neurophysiology who spent his life looking down a microscope for proof that schizophrenia was based on a structurally damaged brain. He died an unhappy, disappointed man as he never found it. I recall one couple — both schizophrenic — who met in hospital, and later married and lived normal lives.

PROFESSOR MURRAY: It is undoubtedly true that some people benefit from psychotherapy. But do they benefit from the specific theoretically-based techniques which the psychotherapist is using, or from the care and attention that they receive from the psychotherapist? The great difficulty has been to bring the scientific method to bear on this whole process. There have now been several studies in the United States, extraordinarily expensive ones, trying to compare interpersonal therapies with supportive or behaviour therapies, and it is very difficult to show that therapy based upon analytical ideas actually works better than the same amount of time spent with a supportive and kindly therapist. Are therapists who interpret the patient's behaviour actually more effective than therapists who are generally supportive?

In relation to schizophrenia, what I am saying is that schizophrenia is a syndrome and that patients develop hallucinations and delusions for a variety of reasons, but within that syndrome there is one severe type of disorder which is associated with developmental abnormalities in the brain.

SIR CHRISTOPHER BOOTH: I would like to support what you have just said. I feel very strongly that it is highly unlikely that psychiatric illness will not yield to the scientific methods that we have been discussing today in the same way that other human diseases have done. This first step in schizophrenia, showing enlarged ventricles, if I may say so, was first shown by Crow and his colleagues at Northwick Park. The pre-conceptions of psychiatry at that time totally denied this in a series of letters to *The Lancet*, saying that schizophrenia is clearly due to behavioural influences. There was a very strong preconception at that time that organic abnormalities of the brain could not occur. Now, this has been challenged worldwide and we are also seeing changes in the neuropeptides in the brain as well. I see that as a very positive scientific approach to the whole disastrous problem of schizophrenia.

PROFESSOR MURRAY: I think we should also blame the influence of neurology because although Sir Denis Hill, professor of psychiatry at the Maudsley, wrote such a letter, the then professor of neurology was David Marsden who also wrote to *The Lancet* saying that the brain changes in schizophrenia were induced by drugs, a view which was soon shown to be wrong.

SIR CHRISTOPHER BOOTH: Absolutely.

PROFESSOR MURRAY: But I agree that Crow and Johnstone's work was the beginning of modern schizophrenia research.

DR E. D. BARLOW: I can assure you that it was not only the psychoanalysts and therapists who resisted the measurement of their results. I worked for sixteen years with Will Sargent at St Thomas's and his intuition discouraged any constructive measurement of the results of his physical treatments. It was a great tragedy at the time.

PROFESSOR MURRAY: One has to ask: why is anti-psychiatry still around? Because there is so much bad psychiatry, and there are many hospitals up and down the country where one would not be treated effectively. The anti-psychiatrists are quite right about that.

DR BARLOW: May I go on to another question? The Mental Health Foundation, as some of you know, has had scientific conferences in Oxford over the last good many years. They are planning this coming year to have one on psychotherapy and my question is whether a scientific — in inverted commas — conference on the subject of psychotherapy is right for development or whether it is premature.

PROFESSOR MURRAY: We have to apply scientific methods to analytical psychotherapy. The behaviour therapists do it in relation to obsessional and phobic disorders. The cognitive therapists are now doing controlled trials on

cognitive therapy in depression. The insurance companies and the new NHS are only going to purchase treatments which can be shown to be of proven value. Therefore if psychotherapy is going to survive and be publicly funded psychotherapists have got to demonstrate their effectiveness.

PROFESSOR TEELING SMITH: I just want to raise what I think is a perfectly good interpretation of the word 'scientific' in relation to the treatment of depression, because although it is entirely empirical it is perhaps the most spectacular of the advances in psychological medicine over the last thirty years which is entirely in fact pharmacological. That is, you do not go to a psychotherapist if you are depressed, not if you are wise, but you do take tablets, and those have been quite remarkably effective, and although we may not know the exact mechanism of it I think we understand quite a lot about it. It is certainly an area where science has, I think, made a major contribution in psychiatry.

PROFESSOR MURRAY: Yes. Psychiatrists were among the first to take up the controlled trial. It is so difficult to prove improvement, that it was necessary to do very exacting controlled trials in psychiatry. Professor Freeman might agree or not on this — the number of depressed people who need to come into hospital for treatment nowadays to have ECT is very small, compared with what it was when I started in psychiatry twenty years ago. Depression is increasingly treated by general practitioners, like pneumonia, and I think we will now see the same development in the management of psychosis because we now have drugs like clozapine which are much more effective in the treatment of schizophrenia-like conditions.

THE CHAIRMAN: I think we must thank you, Professor Murray, for a most interesting paper which, so far as I am concerned, has for the first time made it apparent to me that the introduction is possible of science into this vast field of non-knowing. It has really been most exciting. Thank you very much.

Now we move on to Sir David Weatherall, on the impact of molecular biology. Sir David is Regius Professor of Medicine at Oxford, Honorary Consultant to the Oxford District Health Authority, Fellow of Christchurch, Oxford, Fellow of Magdalen College, Oxford, the Honorary Director of the Institute of Molecular Medicine and the MRC Molecular Haematology Unit at Oxford. His major research contribution has resulted in over 690 publications and these have been concerned with the elucidation of the clinical, biochemical and molecular aspects of thalassaemia and the application of this information to programmes for the eradication of these diseases in different populations throughout the world. For the last four or five years he has been involved with MRC, ICRS, the Wellcome Trust, National Medical Trustees and many other activities.

The impact of molecular biology on medical practice

Professor Sir David Weatherall

The slow change in emphasis in medical research over the last few years from the study of disease at the level of patients and their organs to molecules and cells is the result of the extraordinary revolution in the basic biological sciences which started with the emergence of molecular biology in the period just after the Second World War. Once the basic methods of recombinant DNA technology were worked out it was soon apparent that this new field would have major implications for medical research and practice. And while at first this new reductionist approach to the study of disease appeared to be incompatible with the more holistic form of medicine to which the medical profession and its patients were subscribing, this turned out not to be the case. As human DNA was analysed by the new tools of molecular biology it became apparent that all of us are unique. Furthermore, disease at the molecular and cellular level seemed to follow a similar pattern, regardless of which organ system is involved. Thus, over the last few years this new field has been tending to unify medical research and practice and has started to break down the rigid, watertight compartments into which they had become divided during the earlier part of this century.

Our new-found ability to isolate, sequence, and express human genes, and the possibility of understanding how they are controlled and function in concert to orchestrate cellular function has enormous implications for our understanding of disease processes. So far, we have only scratched the surface of these remarkable new possibilities. But because of the excitement of this field its potential for immediate practical applications has been over-emphasised in recent years. What has been achieved already and what might we expect in the future?

Although it is only about fifteen years since human genes were first isolated and their structures determined, considerable progress has been made in working out the molecular pathology of both genetic and acquired diseases. Some diseases are inherited according to simple Mendelian laws and the environment is of little consequence in their clinical outcome. Others are due directly to environmental factors such as malnutrition, infection, exposure to toxic chemicals, and so on. It is becoming increasingly clear, however, that many of the common killers of western society, heart disease, stroke, major psychiatric diseases, rheumatic disorders, and others, result from the complex interactions of environmental factors with our genetic constitution which render us either more or less likely to develop these conditions following a similar environmental exposure. The development of recombinant DNA technology has enabled us to begin

to understand the molecular basis of disorders which are primarily genetic in origin and, even more importantly, is helping us to start to understand the complex interactions between our environment and our genetic make-up which underlie so many common disorders, the causes of which have hitherto been impossible to determine.

Recombinant DNA technology and medical biotechnology is also allowing us to develop sophisticated diagnostic tests and powerful therapeutic agents. Before long it will allow us to replace defective genes and to interfere with the complex events which lead to cells losing their normal regulatory mechanisms and becoming cancerous. And it has the potential for helping us to approach broader biological issues including ageing, development, and how we have reached our present place in the evolutionary tree.

Because molecular medicine is directed mainly at the study of genetic mechanisms it is not surprising that its first clinical application was for the study of single gene disorders, diseases that can be traced through families in a way that suggests that they are the result of one abnormal gene.

There are over 4,000 diseases which seem to result from the action of single mutant genes. Although many of them are rare, overall they produce a major burden of illness on society; about one per cent of all newborn babies have some kind of genetic defect. Some of them are quite common. For example, in north European populations cystic fibrosis, a distressing disorder affecting the lungs and intestine, occurs in 5-6/10,000 births. Globally, the inherited blood disorders, sickle-cell anaemia and thalassaemia, affect many hundreds of thousands of individuals. The World Health Organisation estimates that by the year 2000 about 7 per cent of the world's population will be carriers for the genetic blood disorders.

Recombinant DNA technology has enabled the molecular basis for many single gene disorders to be worked out. Over the next few years it should be possible to determine the precise cause of most of these conditions, knowledge which can be used for their control and management in several ways. Many of them follow a 'recessive' pattern of inheritance — that is, two defective genes must be inherited to produce a disease. Those with a single defective gene, carriers, are usually unaffected. Knowledge of the molecular defects that cause these conditions allows us to detect carriers and to institute genetic counselling. If both parents carry a defective gene they may wish to avoid having children, or adopt. Or they may choose to have children of their own in which case they can be offered prenatal diagnosis — that is, an analysis of the DNA of a foetus which is at risk, and termination of the pregnancy if the abnormal gene has been inherited from both parents. Dominantly inherited disease, in which only a single abnormal gene is required to produce a disorder, can be identified in the same way. Foetal DNA analysis can now be carried out in the ninth week of pregnancy, or even from cells obtained from an egg after *in vitro* fertilisation.

Although genetic counselling and prenatal diagnosis of disease have been carried out for some time, until recently their scope has been limited. The advent of DNA technology and the ability to identify single-gene disorders will greatly expand the number of diseases that can be controlled in this way. Hence there will be pressures to extend the scope of genetic screening. Already women of appropriate racial background are being screened routinely for the inherited blood diseases such as sickle-cell anaemia and thalassaemia and it seems very likely that screening for cystic fibrosis will become generally available within the near future; other diseases will follow.

Because it is now possible to isolate human genes and the adjacent regions of DNA which are vital for their control, there is great interest in the possibility of replacing defective genes, gene therapy. This can be done in two ways. First, using somatic gene therapy, cells of a particular tissue could be isolated and the appropriate gene inserted into them, after which they would be replaced in the patient. For example, it should be possible to take cells from the bone marrow and replace a defective gene to cure a blood disease. There are many practical difficulties before this can be achieved however. In particular it is difficult to insert genes directly into cells, and some form of transporting system is needed. Currently, human genes are being transferred into cells attached to retroviruses, which have been designed by nature to carry foreign DNA into cells and insert it into their genomes. Although much more work is required to evaluate the safety and effectiveness of this approach there seems little doubt that somatic gene therapy will be developed, at least for a few genetic disorders, in the next few years.

The other approach to correcting a genetic disease, called germline therapy, is different. Here, the idea is to insert genes into fertilised eggs where they would enter many cells including germ cells. In this case they would be passed on to future generations. So far it has not been permitted in the USA or Europe. But the fact that this kind of experiment can be done quite easily in mice or larger animals means that we will have to consider it as we decide on future directions for medical practice. There is, in fact, a simple practical reason why germline gene therapy is not being contemplated at the moment. If it is possible to diagnose genetic diseases in fertilised eggs it should be possible to carry out this analysis after *in vitro* fertilisation and replace only those which do not carry a defective gene.

Many of the common diseases of western society, including heart attacks, psychiatric disease, diabetes and the major rheumatic disorders, have a strong genetic component. They are not due to the action of one gene, but probably reflect variation in function of several different genes which combine to modify susceptibility to many different environmental factors. While there is no doubt that molecular genetics will enable us to define some of the genes involved, why should we want to know?

The real reason for trying to understand which genes are involved in these complex conditions is to find out exactly what their products are, and how their function differs from the same genes in individuals who are not at high risk for a particular disease. This information should help us to understand the cause of these diseases, and hence to prevent and manage them more effectively. For example, supposing that it turns out that schizophrenia is due to the action of one or two genes, if we can understand their function we shall be much closer to working out the chemical basis for this condition and, hopefully, how to treat it. Of course, along the way we may learn how to identify those who are particularly prone to the ill effects of their environments. If so we can focus our public health programmes for their benefit, rather than on the whole population.

It is now apparent that many forms of cancer result from acquired changes in the genetic machinery of cells which lead to their disordered growth. We may inherit genes which make us more likely to develop cancer but most tumours result from mutations that we pick up during our lifetime and which involve oncogenes — that is, genes which regulate cell growth, proliferation and differentiation. For example, common bowel cancers appear to result from six or more mutations; one may be inherited but most are acquired, possibly as the result of exposure to intestinal mutagenic agents. As we analyse cancer in this way it should be possible to develop powerful diagnostic tools and therapeutic agents with which to treat it. Similarly, many distressing developmental abnormalities may be due to acquired defects in our genes. Hopefully, research at the molecular level will enable us to counsel families who have babies with these diseases and may teach us how they occur and which environmental factors can modify our genes during early development.

Powerful diagnostic agents have already been developed by recombinant DNA technology for studying genetic disease. And by utilising the genes of viruses, parasites and bacteria it is possible to generate sensitive diagnostic probes to identify infectious diseases. Similarly it should be possible to develop gene probes for the early identification of cancer and, as described earlier, susceptibility to common diseases such as diabetes and vascular disorders.

It is also possible to insert human genes into bacteria and synthesise their products by utilising the genetic machinery of the bacterial cell. In this way it is feasible to manufacture a variety of therapeutic agents. For example, patients with serious kidney disorders who are maintained on artificial kidney machines are often profoundly anaemic because their diseased kidneys cannot produce a hormone called erythropoietin which is responsible for red blood cell production. Erythropoietin has been made by recombinant DNA technology and is now used to correct this anaemia, an advance which has transformed the lives of many of these

patients. It has also been possible to make other hormones, including insulin, a variety of haemopoietic growth factors, and several effective vaccines. There is no doubt that recombinant human proteins and other therapeutic agents will become increasingly available.

Our evolutionary history is written in our DNA. Thus over the next few years it will be possible better to define our position in the evolutionary tree and hence to understand the origins of man. Similarly, our new-found technology offers great scope for tackling some of the other central problems of human biology including growth and development, the functions of the central nervous system, and the mechanisms of ageing. The medical applications of some of these fields of recombinant DNA research are difficult to anticipate but there seems little doubt that this work will have important implications for the health of future generations.

How long will it all take? The analysis of single gene disorders and its clinical applications for the avoidance of genetic disease is with us now and this field will expand rapidly over the next few years. Similarly, we are close to somatic gene therapy and to the development of many new diagnostic and therapeutic agents. The elucidation of the genetic component of the common diseases of western society will undoubtedly take longer and will require a considerable amount of good luck and ingenuity. While it seems likely that steady progress will be made, it may be many years before the information gained from these studies has a major impact on clinical practice.

Many of these new aspects of medical research will be facilitated by the Human Genome Project. Currently, there are plans to produce both a linkage and a physical map of the human genome by the end of the second decade of the next millenium. A genetic linkage map will provide markers dotted along all our chromosomes at convenient distances apart. This will, in effect, be rather like a road atlas in which all the towns are represented but which tells us nothing about the journey in between them. But it will be of great value for finding genes of medical interest. Filling in the gaps between the towns, the physical map, will involve sequencing the entire human genome. While much of this may be very dull, there is just no telling what unexpected findings will turn up. As well as our hundred thousand or so genes there may be major regulatory regions of great interest, although it seems likely that much of our DNA may have no function and may be just going along for the ride, as it were.

How far can we expect molecular medicine to help us towards achieving a healthier society? It is self-apparent that it should do much to improve the control of single-gene disorders and, possibly, major chromosomal abnormalities. And, of course, it will yield many diagnostic and therapeutic agents and should help us to understand the basis for many forms of congenital abnormality and mental retardation. But what of the

common killers of western society? Current evidence suggests that the bulk of these diseases have a major environmental component. However, when we look at them in an evolutionary context it is clear that they are the result of the action of both nature and nurture. Indeed, there is growing evidence that modern man is ill-adapted to the high-energy, sedentary life that he has evolved for himself over the last few hundred years. Although much of modern medicine is now becoming directed towards the control of the environment and our lifestyles, we simply do not know how far we will be able to prevent and manage our common killers by this approach. Apart from such extreme examples as cigarette smoking, we do not really understand the relative roles of our genes and the environment in generating cancer and heart disease. And in the case of diseases like the major psychoses, rheumatism, autoimmunity, and many others, there is no real evidence that the environment is involved.

The main reason for trying to understand the different genes involved in susceptibility or resistance to heart disease or stroke, or the molecular and genetic basis for the complex changes which occur in a cancer cell, is so that we can start to learn something about the basic mechanisms that underlie them. Except for beginning to understand their environmental triggers, we have made no progress whatever in determining how these diseases are mediated; the various genes involved offer us extremely valuable signposts to lead us to the basic mechanisms involved.

It appears, therefore, that the way forward is through a combined attack, using both the methods of modern epidemiology and the basic laboratory sciences. Indeed, I suspect that they will amalgamate to form a new branch of medical research, which may be called molecular epidemiology. In other words, epidemiologists will continue to throw up clues in the form of environmental hazards which will provide some indication of the genes that will be involved in determining susceptibility or resistance to particular diseases. Progressing in this way, it should be possible to start to understand how many of our common killers are mediated. It seems absolutely essential to try to progress along these different routes; we have no idea to what extent we will be able to control our environments and lifestyles. Furthermore it is still not clear whether diseases such as atheroma and cancer are, to some extent, the results of the metabolic byproducts of ageing.

We should not expect quick answers from the molecular sciences but, in the long term, they should tell us a little bit more about how to control and treat our intractable killers, and hence how to reduce the spiralling costs of health care due to our current 'patch-up' approach to medical care.

TABLE 1 **The spectrum of molecular medicine**

Single gene disorders

Molecular pathology
Screening and prenatal diagnosis
Gene therapy

Genetic component of common polygenic disease

Heart disease. Stroke. Hypertension
Diabetes. Autoimmune disease
Major psychoses. Alcoholism
Cancer
Congenital abnormalities

Diagnostic and therapeutic agents

Preventative medicine
 Screening
 Vaccine development

Broader aspects of human biology and pathology
 Development
 Behaviour
 Ageing
 Evolution

DISCUSSION

SIR CHRISTOPHER BOOTH: David, I would just like to ask you whether you could comment on how you train a young clinician in this field. You have done a lot of work on that.

SIR DAVID WEATHERALL: Yes, we have trained a few. We were talking about this over lunch actually. I do not think one should be too dogmatic about how to train people in this field. What we are really talking about is clinically qualified people. It is just a matter of time, and it takes three or four years of totally uncluttered time to do it properly. My own view is that medically trained people, by and large, have to be very much motivated towards medical science and medicine, and for many of them maybe the best thing to do is to get properly qualified in medicine first. If they are very fired up they can do a PhD first. I am not sure that is the right time. I think it is best to let them do the medical degree first and then have a year or two broadening their horizons in medicine, by which time many of them are in their mid-twenties, and then they can go into the laboratory. I find that by far our best people have done it that way. They are really still fired up and are not totally disillusioned by then, and that is

the time to do it. Now you can do it with an MD PhD programme and it is very interesting to see the results. I think one has to be a little bit cautious of the MD PhD programme because many of the students have very limited clinical aspirations and the vast majority of them are in fact going into full-time science afterwards. So I think one should be flexible. There is the odd young chap who likes to do his PhD straight away and even without doing his house jobs. Everybody is different, but as long as one can find three or four uncluttered years sometime, I am not sure it matters when, as long as it is not too late.

DR SWASH: It has been intriguing to observe the development of genetic localisation of diseases on the genome. Some chromosomes appear rather busy. For example, the XP 21 dystrophies, e.g. Duchenne and Becker diseases, chronic granulomatous disease and Macleod's syndrome are close together on the X Ch, and Down's syndrome, Alzheimer's disease and possibly motor neurone disease are all together on Ch 21. Is this because we know so little, or is there a message?

SIR DAVID WEATHERALL: I do not know whether there may be long stretches of extremely boring genome, but we will not know until we have sequenced them. But my guess is it is rather early to say too much about aggregation, given what little we do know. Within a gene there are some interesting hot spots for mutation and so on, and some interesting kinds of mechanisms for that, but I do not know — it may be pure chance.

PROFESSOR MURRAY: I was thinking about polygenic diseases and what is it that makes progress occur in one and not another. If we had been talking about polygenic diseases in the mid-eighties you might have thought that heart disease would be a good candidate and that Alzheimer's disease would be a bad candidate, but strangely enough there has been some quite remarkable progress earlier on in Alzheimer's but progress in coronary heart disease does not seem to be so impressive. Do you think that is pure luck?

SIR DAVID WEATHERALL: Looking at the data, you could have guessed that heart disease was never going to be easy. I think the concordance rates are round about 20 or 30 per cent in coronary heart disease.

PROFESSOR MURRAY: Alzheimer's disease is pretty low too.

SIR DAVID WEATHERALL: Yes, but we do not know anything much about molecular genetics of common Alzheimer's. You know, you often learn a lot about common diseases by looking at rare variants, and getting in that way. Type 2 diabetes should be the one to break first; it is a genetic disease. If I were going to spend the next twenty years on a disease, certainly I would go for that one rather than heart disease or something which has a much softer genetic component.

THE CHAIRMAN: George Teeling Smith, I am sure you all know, was for ten years in the pharmaceutical industry and then he became, in 1962, the first Director of the Office of Health Economics, and from 1980 Professor Associate in the Department of Economics at Brunel University. He is the author of many books and papers on the pharmaceutical industry and health economics. He was also, may I say, formerly chairman of the International Science Policy Foundation and is, much to my pleasure, a very dear friend.

The measurement of social outcomes

Professor George Teeling Smith

My first real apology is that, surprisingly, as one of the organisers of this meeting, I have got the title of my talk wrong. I am actually going to talk much more about economics than about social matters. But my second is not quite an apology, though you may regard it as such. It is that I am asking you to take it for granted that economics is in fact a science, and looking at the British economy at the moment you may find that difficult to believe! But that is the assumption on which I am working.

I will start with a brief history of the evaluation of medical care from the economic point of view. In the 1930s there were the beginnings of clinical trials, with a steady increase throughout the 1940s and 1950s. Then economics started to come into the picture in the 1950s and 1960s, with what we called cost benefit studies in those days. I will have a comment on that later. But then cost effectiveness studies — and I can explain the difference in a minute — became popular in the 1960s and 1970s and the notion of quality of life, and even though that was regarded as a social matter it is what we have also been concerned with ever since.

In all of these evaluations we are considering the outcome of the medical treatment: we are systematically conscious of the fact that what matters in medicine is what happens to the patient rather than whether or not we feel that we have done a good job as pharmacists or doctors. So clinical benefits were the first benefits that we looked for in the clinical trials, then monetary benefits for the health service, reduced mortality (which again will have monetary implications), improved quality of life and savings for the economy. Those are the sorts of outcome that I am going to be talking about in the next few minutes.

We call the types of study in which we are involved cost minimisation studies, cost effectiveness studies, cost utility studies and cost benefit studies, and I will mention each of those in turn.

A cost minimisation study is in a sense a piece of economic jargon. It is a simple comparison of the cost of two treatments and it has in the past been too important a consideration: is it cheaper to do this, or that? Now that is not a relevant question to an economist, and unless you know whether the outcomes are going to be the same it does not matter whether one option costs ten times or a hundred times as much as the other. If it is doing no good there is no point in doing it cheaply, if the expensive alternative would produce a spectacular benefit. So cost alone is not a relevant measurement.

In cost effectiveness studies we look at the cost of therapy and in particular the savings in other medical costs. But the important thing in

these studies is that the outcomes are assumed to be equal; that is, we are asking which is the most economical way of getting a particular benefit in terms of total costs. One of the great hazards of the past has been the consideration of, for example, pharmaceutical costs, which took no account of the total cost of medical care, or hospital costs or costs out in the community. So we have to look at total costs for cost effectiveness.

There are three simple examples which illustrate cost effectiveness studies. The first is a Swedish study of myocardial infarction which shows that pharmaceutical treatment can be less expensive than non-treatment to achieve the same benefits. This is a commercial for the pharmaceutical industry but these are hard data emphasising the fact that the use of pharmaceuticals does save money.

Then there is a particularly relevant study published in the British Medical Journal about two years ago, showing that although the new preparation carboplatin was more than ten times as expensive as its older competitor, cisplatin, the total cost of the expensive preparation to the health service was less, because it was given as an outpatient procedure rather than as an inpatient procedure, so it avoided the majority of hospital costs and therefore saved money.

The third example concerns the use of third generation cephalosporins rather than cheaper antibiotics or no antibiotics at all in order to prevent post-operative infection. This is a United States calculation showing that the best value in terms of overall hospital or health service costs results from using the more expensive third generation cephalosporins. These are examples of what I would style as cost effectiveness studies, showing that where one cost, in this case the pharmaceutical cost, is greater, you may well get overall savings with the same benefits.

Now I think we have to look at that more closely, and Figure One shows the average cost or the pattern of cost for a patient in hospital. Health service managers are interested in this sort of graph which shows that a particular patient was very expensive indeed early in his treatment. What we have done is to get him out of hospital two or three days earlier when he became an inexpensive patient, well below the average in cost. There are two lessons to be learned from this, the first of which is that it is the marginal, not the average, cost which must be used in economic evaluation. But the second lesson, illustrated by Figure Two, is in the reaction of the hospital manager. He maintains that when we empty the bed it does not remain empty and therefore cheap. Another patient comes in at the most expensive stage of his treatment. So instead of reducing costs we have actually increased them by our simple efficient treatment. Where there was one patient costing on average $\pounds X$, the average cost is now $\pounds 2X$. Costs have doubled; admittedly three times as many patients have been treated, but hospital managers are concerned about the high cost.

FIGURE 1 Hospital cost pattern: inefficient treatment

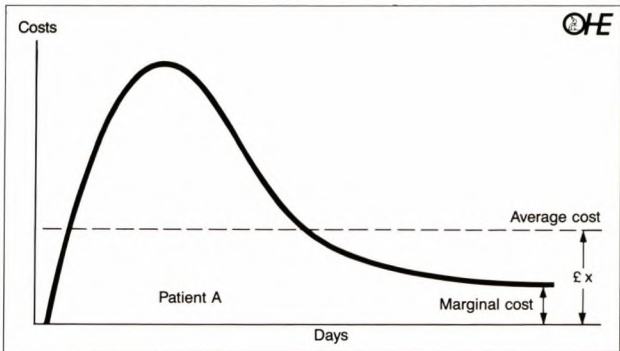
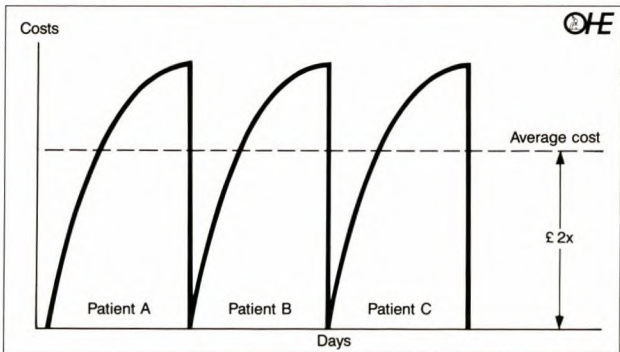


FIGURE 2 Hospital cost pattern: efficient treatment



Happily, we have an answer to that from more sophisticated health economics: we are not going to let them get away with stupid statements. We use what we call a cost utility study, which considers the cost of therapy, minus any savings — that is, the net cost of therapy — and measures it against outcome. This gives a net cost per unit of outcome. What is the cost for a particular outcome? On that basis the previous charts can be re-analysed. In the pattern of inefficient care illustrated in the first of the two

graphs, we treated one patient at a cost of $\pounds X$, and therefore the cost per patient was $\pounds X$. In the second, efficient, care study, we have treated three patients, at a cost of $\pounds 2X$, so that the cost per patient now — that is, the cost per unit of outcome — is only two thirds of what it was under the first pattern of hospital utilisation. This is why we very often have to use cost utility measures in order to assess the real benefit of different patterns of treatment, rather than simply look at cost alone, whether by cost minimisation or cost effectiveness studies.

There is a very good example in the publication of *Pharmaco-economics* at the moment where it is argued that the use of one of the modern genetically engineered products at enormous cost in gram negative septicaemia adds to the cost of treatment, and there is a throw-away comment at the end to say that part of this additional cost is that of keeping patients alive: they were much cheaper when they were dead. Clearly in that particular analysis the authors should have used a cost utility study which would have put some value on survival rather than found that the patient was cheaper when he died. It is too naive an approach. So there are advances being made in this science of health economics all the time.

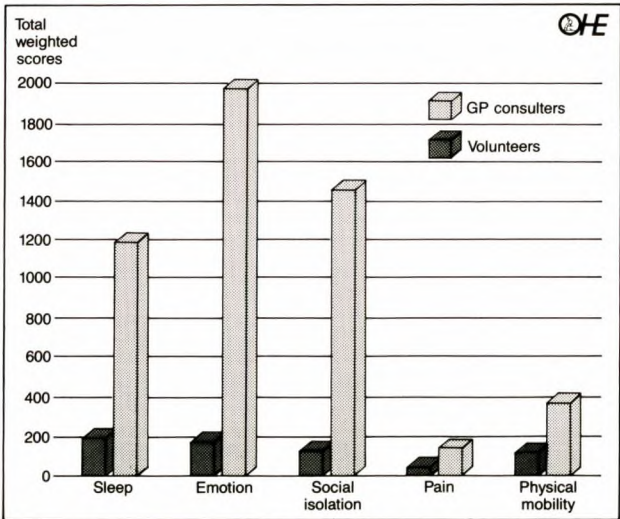
Another example of a cost utility study shows how very much cheaper it is to use one of the modern statins to reduce cholesterol rather than the older (and, to the patient, extremely unattractive) preparation, cholestyramine, which was a sort of glass of mud which you drank in order to lower your cholesterol. Simvastatin tablets are not only more pleasant for the patient but also much more economical.

However, mere survival is not by any means the only outcome in which we are interested. We have most recently started to include in our calculations a measurement of quality of life. The two tools which we use are the health profile which shows a pattern of health on various criteria such as pain or mobility and gives a profile of the well-being of the patient, and a health index which gives a numerical value for well-being.

Figure Three is an example of a health profile. This is a study comparing patients who summon their doctor (illustrated by the shaded bar) with normal healthy patients (shown by the darker bar). The height of the bar measures the degree of disability and distress suffered by the patient, and it shows, rather reassuringly, that patients who were ill were considerably worse off in terms of quality of life than those who were well. It would have been remarkable if it had been the other way round. That is just an example of a health profile.

A health index, on the other hand, gives ranges of defined states of health each of which is given a value. One way of allocating these values is the most up-to-date, delightfully named Euroquol; this is one of the areas where Europe has been able to cooperate successfully across the frontiers in producing this measure of quality of life which is claimed to be applicable in all of the European countries which cooperated in pre-

FIGURE 3 Nottingham health profile scores for GP consultants and controls



paring it. It considers six criteria — mobility; self-care; the main activity of the person; their social relations; their degree of pain; and their mood — and then their score, from either 1 to 3 or 1 to 2. In Table One you

TABLE 1 Euroquol

Health status value for different health states

All highest		100
Main activity	: 2/2	} 65
Pain	: 2/3	
Main activity	: 2/2	} 35
Social relationships	: 2/2	
Pain	: 3/3	
Mood	: 2/2	
All lowest		1

2/3 indicates that the patient is suffering some pain:

3/3 indicates that the patient is suffering extreme pain

can see the values for different states and the values put on them by panels of 'experts'. The highest score is 100 where the patient is suffering no disability. The second case has the patient with the lowest score for their main activity, and for pain: they are in the second of the three classes. Their score is 65. Where there is a range of handicaps, and main activity, social relationships, pain and mood are all affected, their score is down to 35. If all of the scores are in the lowest category they score just one. So that is an example of the numbers that are given for different health states.

That index underlines what I have just said; a score of 65 is therefore the state where a patient is unable to perform any main activity and is suffering moderate pain, and with a score of 35 the patient cannot perform any main activity, cannot pursue family or leisure activities, is in extreme pain, and is also anxious and depressed. Hence the score of 35. That gives some idea of the use of a health index in measuring quality of life.

Now I said that I would mention a quality of life adjusted year. This is something I am sure many of you are familiar with: it is a question of simply multiplying the number of years of life of the person by a factor relating to how well they are. So that if, for example, they live for 10 years with only 50 per cent well-being they score only 5 quality-adjusted life-years. On the other hand, if they were 100 per cent healthy for 10 years they would score 10 quality-adjusted life-years. If they were dead they would score nothing. So this is a way of combining survival with well-being.

Table Two was produced by Alan Maynard from York a couple of years ago in which he gave the cost in relation to quality of life for a large number of different interventions, and you can see that these range from very low costs where cholesterol testing and diet alone in the high-vulnerability group of males costs only £200 per quality-adjusted life-year, to, at the very bottom, surgical intervention for cancer of the brain where you are into the hundreds of thousands of pounds per quality-adjusted life-year. The Maynard argument, strongly challenged by many people, is that there should be a cut-off point and that where the cost relative to quality of life is too high the treatment should not be available. That has been attempted in the United States with the so-called Oregon experiment where a ranking was produced for a large number of different procedures in order to establish a cut-off point for the Medicaid services in Oregon; those treatments which were too expensive in terms of the benefits provided would not be available. The Oregon principle looks like being accepted by the Clinton administration, despite its limitations. I certainly do not support the Maynard view that this is the answer to the application of health care resources. I think it is interesting, but I do not think it is a determinant of what should or should not be available.

TABLE 2 Treatment costs at 1990 prices in £ sterling (after Maynard 1990)

Treatment	Cost/QALY (£)
Cholesterol testing and diet only (all adults aged 40-69)	200
Neurosurgical intervention for head injury	240
GP advice to stop smoking	270
Neurosurgical intervention for subarachnoid haemorrhage	490
Antihypertensive therapy to prevent stroke (ages 45-64)	940
Pacemaker implantation	1,100
Hip replacement	1,180
Valve replacement for aortic stenosis	1,410
Cholesterol testing and treatment (all adults 40-69)	1,480
CABG (LMD severe angina)	2,090
Kidney transplant	4,710
Breast cancer screening	5,780
Heart transplantation	7,840
Cholesterol testing and treatment (incrementally, all adults aged 25-39)	14,150
Home haemodialysis	17,260
CABG (1 vessel disease, moderate angina)	18,830
Hospital haemodialysis	21,970
EPO treatment for anaemia in dialysis patients (assuming 10 per cent mortality reduction)	54,380
Neurosurgical intervention for malignant intracranial tumours	107,780

CABG — Coronary Artery Bypass Graft

LMD — Left Main Disease

EPO — Erythropoietin

Source: Maynard 1990

This brings us to the last type of analysis, the true cost benefit analysis. Whereas we used this phrase rather naively at the beginning, now we regard it as a comparison between all the costs involved and all of the benefits. So, if we look at the difference between the 1960s definition of cost benefit — simply savings to the health service combined with savings to the national economy — and the 1990s definition which includes a measurement of the quality of life, we see a very complicated process at work. I will conclude with a discussion of one way in which the quality of life can be measured in monetary terms.

The willingness to pay is one example which I want to talk about, by considering the patient's own estimate of what they would be prepared to pay for the benefits of a successful treatment or perhaps the taxpayer's evaluation; as you can imagine the patient's estimate of what they would be prepared to pay and the taxpayer's estimate of what they would think it appropriate to have to pay may be very different. There is not a gold standard in willingness to pay. Nevertheless, we recently asked parents of under-sized children what they would be prepared to pay for the treatment of their children with human growth hormone, and we found that in the highest income group, over 35 per cent of the wealthier parents

said that they would pay more than 30 per cent of their income in order to obtain the treatment for their child if it were not available, free, on the National Health Service. These parents were putting a very high value indeed on the treatment of their children with growth hormone. But I must emphasise that this was a survey of the parents of affected children, so they had a high degree of self-interest in deciding what they would pay, and the study drew attention to the fact that this was only one evaluation which could be placed on this hormone treatment.

So let me just end by reminding you of the outcomes that I have been looking for in this sort of socio-economic analysis of benefits in this new science of health economics: the clinical benefits, the monetary benefits to the health service, reduced mortality, improved quality of life, and savings to the economy.

Could I remark in conclusion, if perhaps health economics does not yet seem to be a science, where economic evaluations are meaningful and justified, that almost exactly twenty years ago a very distinguished pharmaceutical physician said in an article in *The Lancet* that the double-blind trial should be thought of as having feet of clay, and that whereas most of us, thirty years ago, thought that the double-blind clinical trial was indeed the gold standard for clinical evaluation, it was not altogether accepted. I think that health economics is in that state now, and that people are perhaps a little sceptical about it, but I believe that in ten or twenty years' time economic evaluation of medicine will be regarded in just the same light as routine clinical evaluation is regarded now.

DISCUSSION

THE CHAIRMAN: May I just throw this question directly at Professor Booth: do you think that the Teeling Smith statement regarding health economics as a new science is a valid one?

SIR CHRISTOPHER BOOTH: You are posing me that question — he is a friend of mine!

THE CHAIRMAN: Never mind. We are questioning scientific truth.

SIR CHRISTOPHER BOOTH: I think we face a very difficult question here. Sir Peter Medawar always said that there were, I think, three areas that soothsayers were basically involved in. One was economics, the second was meteorology, and the third was prediction of the future. I tend rather to share that view, and feel that if we take economics as a science it certainly does not match up to my definition of what a science is, nor do I think that in this country economists have been exceptionally successful in helping either our government or our organisations in determining their future. So I

was murmuring when you asked me to comment, and I would need a lot of convincing that health economics was any more of a science than straight economics. But perhaps I could ask George to define what are the scientific elements of economics that equate them at all to science.

THE CHAIRMAN: Before he answers that: you spelt 'straight', in 'straight economics', s-t-r-a-i-t, did you?

PROFESSOR TEELING SMITH: I think the answer is that health economics fortunately are less uncertain than macro-economics for the economy as a whole. My argument is this: before we actually do something — and this is why I was, if you like, criticising Alan Maynard — we should at least try to measure the value of it, if we can. I do not think that even our measurements are gold standard measurements.

Just as we had different definitions of schizophrenia from Robin Murray, so there are different definitions of quality of life. I showed the Euroqol, but I could have shown a slide that gave different values of the same state using different methods. So we do not have a gold standard even for our measurements, but we acknowledge that and we publicise that fact. I did not happen to publicise it today. I am doing so now.

But my argument is, that measurement, which is what I have been talking to you about, is important, and my analogy is a very simple one. If you went on a long hike on a hot summer afternoon, aiming relentlessly for a particular destination, and you felt thirsty and there was a signpost indicating a hotel down a side road, the decision as to whether you walked down that road to have the drink would depend, or ought to depend, on how far away the pub is. If it were a hundred yards down, you would certainly decide to go. If, on the other hand, it were fifteen miles down the road, you might well be extremely reluctant to make the extra journey. Unless you knew how far it was down that road, you could not make a logical decision. What we, as clinicians and scientists and managers, aim to do in health economics is to give you information on which to base your decision. We do not, as do some macro-economists from the economy as a whole, try to tell you what to do. We simply tell you what is going to be involved in the various options.

MR MAYNE: I would like to consider further the question of how reasonable it is to measure supposed quality of life in terms of people's ability to pay for it. When I saw the figures of willingness to pay for medical treatment in relation to family income, my strongest impression was that those with high disposable family income were much more willing to pay a given proportion than those with low income. It seems fairly easy to explain this by supposing that those with low family income are very reluctant to pay even small amounts because they find it really hard to meet their basic needs. They might find that they would have to sacrifice

some of their basic needs by paying even 1 or 2 per cent. A high-income family would experience no such problem in paying a similar proportion of its income.

Therefore I think that extra benefit needs must be viewed in relation to basic needs. Here there is a hierarchy which puts basic needs like food, clothes and shelter right at the bottom. Health needs would come second, and then various other needs. So most people would probably decide that if health needs were going to compete with food and shelter as items of expenditure, they could not opt for the health needs. That would be my observation on those particular figures.

PROFESSOR TEELING SMITH: I think the answer to that is that we did show the range of figures. I think it is just as significant that people with very low income were still prepared to spend 5 or 10 per cent of their income on health as that people with high income were prepared to spend 30 per cent. I think both sets of figures indicate the value that people put on health.

MIR MAYNE: I am not disputing your judgment as to the way people would actually decide. I was just putting my interpretation.

DR HOPKINS: As a family doctor I also have to consider the quality of the life of the patient's family as well as that of the patient. I think this is something which the economists have not dealt with, and there is not much evidence of it here. And certainly not in the United States of America either, if a book written by a professor of bio-ethics which I was asked to review some time ago, is anything to go on. As you probably know, they have in many American hospitals teams comprising the doctors concerned, a nurse, the hospital accountant, perhaps a religious person, and also someone from outside the hospital; they go around each week to evaluate the validity and value of continuing to treat Joe Bloggs. They have already spent \$100,000 on him; he is 68 or more, married or not married, he has children or has no children, he works or does not work — all these factors are taken into account and the team makes its decision so that no one individual is responsible for the outcome. They might decide that he really does not justify the outlay of another \$50,000. This is audited of course, and worked out rather as Maynard's analysis is, but I am glad to hear you say that the American government has come out against this practice. But sadly it seems that we are getting near to rationing health-care by economic measures here in the UK.

On a personal note, I developed a cancer in my oesophagus eighteen years ago. The chance of my surviving that was pretty remote. But I went through seventeen operations in as many months, in spite of the very poor prognosis with regard to my survival. I shudder to think what might have happened to me, had an economist been involved, and had this system been in action. I am quite sure that in view of my extremely poor

prognosis, nobody would have been allowed to operate on me, nor for me to occupy a hospital bed for the seventeen months required before I was fit to return home and to work.

PROFESSOR TEELING SMITH: I do feel that it was essentially a clinical decision to proceed with the operation, and I am so glad it was successful. It was not primarily an economic decision. I think that they made the right clinical decision to go ahead.

DR HOPKINS: Strangely, the next six patients to be treated for this disease, died soon after their operations. But this is the point — even a very good surgeon can still encounter conditions which are notoriously difficult to cure.

DR LESLEY ROGERS: I just want to be clear about your criticism of the Oregon model and of what Alan Maynard is apparently trying to do. Do you feel that the models are not sophisticated enough to warrant the prescribing of a cut-off line for treatment, or do you object to the line on principle?

PROFESSOR TEELING SMITH: I think there are two answers to that. First of all, I do not think the model is sophisticated enough. For example, our researchers do indicate that the things at the top and the things at the bottom are very different but small variations are of very uncertain significance. The second reason for not using it is the ethical/social one which is that economics must not be the determinant of health care. The purpose of medicine is not to save money but to make people feel better. The Oregon experiment fell down in the local press in Oregon when a baby needing a kidney transplant was ruled to fall below the line on the grounds that she was easily replaceable and that there was no reason to do the operation. You can imagine the outcry that would result in any country if it were announced that, on economic grounds, this operation would not be done because the child was not worth saving. Emotional and certainly ethical factors come into consideration as well and, as I say, we absolutely do not regard ourselves as God-like in the field of health economics.

THE CHAIRMAN: Thank you very much, George. Just before we close, two thoughts. The French poet, C eline, who is a great favourite of mine, wrote:

'Tout ce qui est int ressant se passe dans l'ombre.

On ne sait rien de la v ritable histoire des hommes.'

It seems to me that what we have done today is reveal some of the true history. To sum up, I think that a future agenda for research must provide a reasonable perspective of the present role of science and technology in medicine, and we have also to lay down or deal with the long-term

humanistic and social questions. Without that understanding, this day would have failed, and I must express my thanks to the Office of Health Economics for having made it possible for this very interesting event to occur. Thank you very much, George.

PROFESSOR TEELING SMITH: Thank you very much indeed for your chairmanship.