

Selected lectures

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Harveian Oration

Science, society and the perplexed physician

This lecture was given at the Royal College of Physicians in 2000.

Imagine it is the year 1600, just 400 years ago today. Elizabeth I is on the throne, Oliver Cromwell is one year old, Shakespeare has just written *Hamlet*, the population of England and Ireland is around five and a half million people, and William Harvey is just 22 years old and studying in Padua for his doctorate. And it is there that the great anatomists were revealing the structure of the human body, and the mysteries of the heart and circulation were beginning to take the attention of William Harvey. By 1615 he had all the evidence he needed to demonstrate the way the blood circulated around the body, pumped by the heart

But when he rushed into print, about 13 years later, his discoveries were greeted with some indifference and it took many years before his ideas were eventually accepted, except I believe in France.

Part of the indifference was due to the fact that there were no obvious, practical, beneficial outcomes from his findings. Neither Harvey nor anyone else had any idea about the manifestations of heart failure. It was another 100 years before it became possible for anyone even to measure the blood pressure, and it was over 200 years before the clinical value of his findings started to become clear. So it does seem that scientific discovery, profound as it may be, and nowadays would be heralded as a breakthrough, is always handicapped by the associated areas of ignorance that limit our ability to understand and take advantage of those findings. So when I choose to take a forward look as to what the future holds for doctors and patients as I intend to do in this talk I hope you will understand why I will not put a timescale on the sort of predictions I will try to make and in any event I am sure I am not going to divert this audience from its healthy scepticism.

The title of my talk includes the phrase, 'the perplexed physician', because perplexity seems to characterise the state of mind of many of my beleaguered colleagues, colleagues not only here in the UK but elsewhere around the world. And that perplexity derives from the pace of change in the world in which we operate and from the vertigo induced by shifting grounds and moving goalposts with which we are faced. The need to cope with the expanding fields of science and information technology at a time when society itself is also changing rapidly, in ways which are not always beneficial, is stressful for many. The changes are not only influencing the tools of medicine, the drugs and technology, but also the ways in which we practise.

And all of this is coupled to the fact that physicians are never far from the firing line when criticisms of almost everything we do seem rife. And behind it all is a sense that we have lost control, if we ever had it, and not just of what we do for patients. As patients have increasing access to home diagnostic, near patient tests and the internet provides them with all they will ever need to know about their diagnosis and treatment, who will need physicians? Is it too remote to imagine that physicians will become largely redundant before the end of this century? Well I hope by the end of my talk to offer a little reassurance, to the physicians amongst us, that we will continue to have a role to play, perhaps not the same roles as now, but important and distinctive ones nevertheless. But the fact that I feel obliged to even raise the spectre suggests that there is little room for complacency.

So I will talk about the impact the remarkable advances in science have, on the one hand, and, on the other, the no less remarkable impact of the shifts in society which are likely to have quite opposite effects on doctors and patients.

I hope that the advanced thinkers in the audience will forgive me using such an archaic term as 'patient' but I only do so because I perceive a clear difference between patients and clients, customers or mere users of the service. The word patient suggests a certain vulnerability that is missing from the customer/supplier relationship and poses an extra requirement from that relationship. I shall return to this because it seems to me that paradoxically the more information that is available in the public arena the more vulnerable and anxious people have become.

So my thesis will be, as you might guess, that doctors will turn back to the basic characteristics that have always been required of them: to be caring individuals with a broad-based knowledge of human behaviour both physiological and psychological, and who know how to weigh all the evidence in the balance in which a specific patient sits right at the fulcrum. But let me fill in the time before I tell you that by exploring why it is possible to reach this rather less than revolutionary conclusion.

How do these two major forces, scientific progress and societal change, have such an impact on physicians and their activities?

I recently happened to be sitting on a platform with a prominent politician who was saying some rather less than complimentary things about scientists for one or other of the many reasons that they may be berated. Then he happened to notice that I was sitting next to him and he kindly said, 'Oh! Of course he's all right, he's a doctor'. Now I wasn't quite sure whether to take this as a compliment for not being a scientist, but I suppose like most politicians' remarks, you can take them to mean what you want. But the serious question here is, where will the doctor sit in relation to the march of science?

Making predictions in the medical sciences has always been fraught. Who would have thought 20 or 30 years ago that duodenal ulcers were caused by an infection in the stomach and you could cure them with a short course of an antibiotic? All I know is that if you would have suggested this seemingly remote possibility at the time I was taking the MRCP examination you would have failed the membership.

To have predicted our ability to eradicate polio from much of the world, to transplant organs, to replace joints with prostheses, to implant hearing devices in the cochlea at the time when I graduated would have required extraordinary perception. So projecting what medical science will bring us in 20, 30 or 40 years time must be equally fraught. I think Kierkegaard got it right when he said that 'life has to be lived forward but can only be understood backward'.

Nevertheless the direction of change is clear and the scientific community is eagerly anticipating the fallout from the Human Genome Project that was announced with such a beating of drums in June. [Here I showed a photograph from *The Times* of President Clinton in the foreground and Tony Blair, out of focus, in the background.]

Here we see President Clinton giving out the good news and predicting the cure of all man's ills, and here, in the background, perhaps recognising a degree of hyperbole in the pronouncements, stands the shadowy figure of our own brave leader.

Now I suspect that you like me may have heard more than enough about the marvels that the Human Genome Project is going to bring us, so I will not dwell on these save to highlight some of the more realistic goals insofar as they are likely to impinge on the need for physicians.

An understanding of individual genetic variability, derived from knowledge of the complete human genome will give us the ability to understand the genetic basis of disease. Leaving aside the defects in obvious single gene

diseases, cystic fibrosis, Huntington's disease and the like, knowledge about those multiple genes which increase susceptibility to a number of common diseases – diabetes, cardiovascular disease, hypertension, cancers and mental illness – will become available, but also immunological and even infectious diseases. It is becoming increasingly clear, more than perhaps we realised, that there may be a microbiological basis for a number of common diseases, including some cancers and cardiovascular disease. Genetic susceptibility to infection and reaction to infection is a fascinating area of work.

So we will have a handle on who is liable to suffer various common diseases and why, and this in turn opens up the possibility of taking preventative measures. The gene only recently shown to play a role in type 2 diabetes, the common form of the disease, opens fascinating prospects. In addition to all that, the genetic basis of behavioural and psychiatric disease might become more obvious. That type of information about the anatomy of the human genome provides us with a basis for diagnostic and therapeutic targets. The pharmaceutical industry is investing vast amounts of money into pharmacogenomics not only in a search for new therapeutic targets but also to get a grip on the genetic basis of variability between patients in the way they respond to drugs. Hitherto major advances in therapeutics have been achieved by taking advantage of an understanding of receptors on cell surfaces, and designing drugs that either stimulate or block the actions of those receptors. There are several hundred receptors but this figure pales beside the fact that there are several thousand peptide or protein products of specific genes that are themselves potential new drug targets. This enormous expansion in potential therapeutics is stirring the doves of the pharmaceutical industry.

And then there is the genetic basis of variability in responsiveness to drugs which is extremely valuable if you want to target drugs to those who are likely to respond best and of course to avoid giving those drugs to patients who are genetically predisposed to suffer adverse effects. Knowledge of the relevant genes in the population at large would then allow the very focused prescription of drugs to specific individuals within that population. The new sciences of post-genomics and proteomics are opening up as it is increasingly recognised that knowledge of the genes themselves is but the first step. We have, ahead of us, years of scientific endeavour as we try to understand what these genes actually do, what proteins they code for and how they in turn work.

If we now combine information about our genes with advances in microchip and information technology we have an extraordinarily powerful set of tools. Microchip technology has advanced at an awesome pace and it is now possible to utilise it in diagnostic tests. The GP faced with a patient with

a sore throat will be able to tell immediately if it is due to a streptococcal infection or not, by using a simple test strip placed in the saliva and furthermore will know what subtype it is and its antibiotic sensitivity. It will soon be possible to test a patient with a febrile illness to see whether they have influenza or not by a simple bedside test

Near patient testing will undoubtedly advance rapidly over the next few years and as a result pathology laboratories are likely to be changed radically in the sort of work they will be asked to do.

Now these developments will not only place the prospect of remarkable diagnostic and therapeutic tools into the hands of doctors. They will also make them available to others such as pharmacists, corner shops, railway stations and in supermarkets, but they will also be placed in the hands of patients themselves, at work and in their homes. There are already prototypes of home computerised systems that can make it easy to keep a check on how patients are doing.

There is enough DNA in a simple mouthwash to test for all the genes of interest. Furthermore, it is possible now for individuals to send off some mouth washings to a laboratory for them to test and send the result back in a day or so. For example, a woman with a family history of breast cancer can test herself in this way to see if she carries one of the breast cancer genes. Furthermore it will not be too long before chip technology becomes so automated that the equipment becomes freely available and, for example, sited in your GP's surgery.

It does not seem beyond the powers of imagination to envisage a situation in which individuals carry with them on a little data card, information about their own genetic variations which make them susceptible to certain illnesses, their liability to adverse reactions to drugs and their need to contain their lifestyles and to avoid activities which are particularly risky to them. It is also possible to imagine a situation in which you will have your annual 10,000 miles service, and a battery of diagnostic tests applied, any defects detected will be managed at a pre-symptomatic stage by relevant adjustments or drugs, which by then will be capable of switching genes on or off without the need to dream up improved techniques of gene replacement. It is even possible I suppose to imagine a time when we will have within ourselves the capacity to delete errors, to self-correct diseases, rather like space shuttles seem to be able to do now. I understand that the top range of Mercedes-Benz cars can electronically detect their own little errors, diagnose them and correct them as you drive, so to speak.

Now you might think that all of this is rather fanciful and you could be right but I hope you will grant me just a little extrapolation. Of course the

timescale over which these advances will be transcribed into practice is unclear but my guess is that it will not be quick and certainly not immediate for many of them.

Then there is the internet. We now have vast amounts of background information available to everyone, about every illness from which they are likely to suffer. There are now available large numbers of reliable, and even more unreliable, sources of information about the nature of specific illnesses, the meaning of diagnostic tests and the therapeutic options. There are very many of these. One of the interesting names I saw the other day was 'get well quick.com'. So it may not be easy to know which are the best sources of information but no doubt, in time, this too will become clear. Only the most computer literate at the moment, admittedly an increasing proportion of the population, have access to this sort of information but there seems no reason why such access will not become universal in the not too distant future as the means of delivering it becomes simpler and requires less and less computer know-how.

And now we're beginning to see commercial organisations providing medical consultations and advice on the web. I've heard of one which is offering personal advice to cancer sufferers and it seems entirely likely that this type of internet advice will grow whether we like it or not.

So what does all this mean to the man on the top of the space age Clapham omnibus? Will he feel secure in the fact that he knows his genetic make-up, his susceptibilities, his behavioural characteristics, and with his ability to detect disorder in the fine workings of his mind and body, and furthermore have ready access to information technology which will allow him to take corrective action? And what does it do to the physician who even now feels threatened as the mystique of medicine is lost? Patients, who are already armed with computer printouts, will also have all their test results, diagnostic possibilities and therapeutic options in their hand as they come through the door. Not only that, the patient is more intimately and personally interested in the details of such information about themselves, and may well have done more research on it than the doctor can possibly hope to match. The ready access to all the necessary information about their illness and its treatment places in the hands of patients considerable power of self-determination. Hence my question of whether there is a need for physicians at all in this brave new world.

I asked a group of patients I met recently whether they thought there would be a need for doctors in light of these potential developments and they thought for a while, then one of them said, 'Well I suppose we will always need a second opinion.'

So there seems to be some hope for us then. But there may be even greater scope because, at the same time as this scientific revolution is going on, there are parallel changes occurring in society at large and which, paradoxically, may increase rather than decrease the need for guidance and mentoring roles in the shape of physicians. Apart from a population that is increasingly knowledgeable as I have described, there are two other sorts of societal changes that are interlinked and which potentially make life difficult not only for the perplexed physician but also for the perplexed population.

Firstly, the confidence and trust by the public in science in general and in doctors in particular, has been sorely shaken and is at a low ebb, at least according to the media. Secondly, a public that is increasingly risk-averse and increasingly concerned about their health at a time when they have never been healthier.

Trust in doctors is inversely related to the scientific basis of our practice it seems. We were accorded most authority when we least deserved it. The rising interest in complementary medicine, the scientific basis of much of which is somewhat sketchy, attests to the lack of correlation between public trust and the scientific evidence for what we do. Suspicion and mistrust is reflected in the rising numbers of cases of litigation against doctors, regularly inflamed by the media. This is belied by the public opinion polls that show widespread trust of doctors despite the news stories. While the media may portray medical disasters as the tips of large icebergs, patients tend to be content with their doctors. Clearly it is important not to confuse patients with the public at large or the media, each of which express quite different opinions. Of course there is little room for complacency but it is important to retain a sense of perspective.

Rather more interesting is the public's attitude to risk and safety, illness and death. According to Theodore Dalrymple, who wrote that marvellous book entitled *Mass listeria*, the healthier we are the more we fear the risk of ill-health, and the longer we live the more we fear death. The phrase 'the worried well' he suggests characterises modern society. Let me quote from him: 'Death is an anomaly which requires an explanation. It is an injustice. So indeed is illness. Illness strikes without regard to the virtue of its victim and if life turns out to be unfair, as it always does, human benevolence must be to blame. Death these days is someone's fault.'

And again he says: 'when men are responsible for everything, even the existence of death, there is no room for sadness, only bitterness.'

He goes on to point out that the universal declaration of human rights more or less states that everyone has a right to perfect health. The WHO definition of health is not merely the absence of sickness but the presence of a

state of well-being. The natural state of man in other words is not only to be alive but also to be healthy.

Of course the problem is that we all fall short of that. No one seems to be really healthy. Statistics from the United States are absolutely frightening. Harry Glassener in his marvellous book *The Culture of Fear* added up all the diseases from which Americans are said to suffer, and found that out of a population of 266 million Americans some 543 million have some serious illness, that is, nearly twice as many Americans have diseases as there are Americans.

As new risks seem to spring up so new diseases with new diagnoses come along. Apparently one in eight children in New York is handicapped in one way or another. When they are obese they are suffering from an eating disorder. When they are shy they have a social phobia. When they get poor grades in school they have an academic achievement disorder. Have you noticed the way in which the new disease of 'sex addiction' has reared its head? Apparently 10 to 15 per cent of Americans suffer from it, if they can be said to suffer.

You may not think that this is a serious issue but the point about having a name for a condition suggests that there must be some cause and there must also be a diagnostic test and some treatment.

Everywhere there appear to be risks, dangers and hazards that, despite the evidence, seem to be increasing rather than the reverse. Frank Furedo in his book also interestingly entitled *Culture of Fear* suggest that risks are everywhere, from *Listeria* in cheese, heavy metals in fish, *Salmonella* in chickens, insecticides and fungicides on vegetables and fruit, hormones in meat, holes in the ozone layer, and GM foods. Conventional crops are being contaminated with GM pollens and organic foods doused in faecal organisms. Where then shall we turn for our food?

A survey carried out first in 1947 and then again in 1996 about people's eating habits showed that while in 1947, 80 per cent said they could eat what they liked, by 1996 this figure had dropped to 58 per cent and the number who said that they had to take care with what they ate doubled from 20 per cent to 41 per cent. Now the chattering classes would not dream of drinking tap water. Who knows what's in that? The growth of the bottled water industry speaks volumes.

The safety business is a growth industry. Schools and hospitals increasingly resemble minimum-security establishments. It is difficult to know how we have managed to survive. As Ulrich Beck has said: 'The sources of danger are no longer ignorance but knowledge'. Or as Theodore Dalrymple put it: 'Knowledge without perspective is just a higher level of ignorance'.

Yet somehow we do manage to survive. Average lifespans are increasing all the time. The expected lifespan of Britons at birth throughout this last century have shown a gratifying and continuous rise. One interesting side-line on this increase in life expectancy was cast by John Bunker in some important work, in which he demonstrated that more than 50% of the extra life gained by the population has been the result of improvements in medical care and most of that has occurred since 1950.

But what the risk-averse population sees is not long survival but the potential for death. Death rates remain, persistently, despite all our efforts at exactly 100 per cent. Everyone dies. If you make a list of the major causes of death in the UK, cardiovascular disease and cancer head the list. But it is the bottom line, the total, that will always be 100 per cent. The difficulty is that if we somehow managed to cure or prevent cardiovascular disease or cancer, then it is inevitable that the percentage of the other causes of death will rise and perhaps create more anxiety about the apparent growth of these risks.

Now you may ask where do I get this idea of a public consumed by anxiety and worry? Well from the newspapers of course, where else? The reasons why provocative headlines appear is not difficult to understand since they have been shown to sell newspapers. As newspapers have become highly commercial and competitive they have developed a culture of reporting in terms of 'the biggest', 'the best' or 'the worst ever' disaster and break through because panic sells papers while a cause for peace of mind does not. Do the media reflect the views of the public at large, the silent majority? Whenever there is a poll of public opinion the results suggests something else. This is not to say that the public is not confused but rather that it tends to reserve judgement and remain uncertain.

In summary then, I can pose a series of paradoxes which form the twin horns of the dilemma facing the perplexed physician. The public is more knowledgeable but more confused, more informed but more worried, more independent but more reliant on others. They are living longer but are increasingly worried about dying. They are healthier but more concerned about ill-health. The environment is cleaner but the public seem increasingly anxious about environmental hazards. The more they understand about science the less confidence they place in it. The public is ever anxious to utilise the fruits of scientific endeavour in general, where it leads to new treatments and cures in particular, but they are increasingly mistrustful of science and scientists. The more evidence-based medicine becomes the more the public turns to complementary and alternative medicine, much of which is not evidence based. They are more dependent on experts but less trusting

of them. The public wants certainty when choices almost always have to be made in the absence of certainty.

Does all this then suggest that there is less need for physicians? I cannot help believe that in the face of a confused population, increasingly concerned about their health, the need for physicians will increase rather than the reverse.

But what sort of physicians should we become? The type of patients I have described will require many of the characteristics of physicians that are unlikely to seem novel. Physicians will certainly need to have a wide range of abilities. Indeed the major characteristics of future physicians will be their ability to bring a perspective from an understanding in depth of their own specialist area, but increasingly also in the breadth of medicine and society. One of the chief characteristics will be an ability to assimilate and analyse information and importantly to make decisions and offer choices in the absence of certainty. For all these reasons we will need to continue to attract into medicine the brightest young men and women. They will have to have the ability to sustain a very long training programme through undergraduate and postgraduate careers that are required to gain that degree of breadth and perspective. We are unlikely to need fewer physicians of the type who have the ability to bring a broad perspective to patients' needs and combine that with a full understanding and knowledge of the scientific basis of medicine.

Now I regard those features as essential but not sufficient. If those abilities are to be applied to patient care it is equally important that physicians are responsive to their patients' needs in communication, empathy, compassion and a sense of partnership, so the patients feel that they have some control of the relationship with their physician. The increasingly confused population, bombarded with vast amounts of information, is likely to need more of those characteristics rather than less. They are at least as essential as a deep understanding of the scientific basis of medicine and currently we may be falling short of that ideal, largely I believe because of lack of time. But that is another story.

Perhaps I could also say one or two words about the partnership between physicians and patients that is spoken of so glibly. To me this partnership is clearly one of unequals in a number of respects. The doctor, no matter how empathic, cannot fully appreciate the patient's symptoms or suffering, and the patient cannot have gleaned that perspective which is in the hands of the doctor. You may remember that great American physician Frank Ingelfinger, the late editor of the *New England Journal of Medicine*, who gave a marvellous lecture that was published in his journal and entitled 'Arrogance', in

which he pointed out that physicians cannot afford to be arrogant simply on the basis of their presumed superior knowledge. But he also pointed out that the greater arrogance was that of the ignorant who feel that they can pontificate despite a lack of knowledge. More importantly, he also suggested that while it is important to be able to offer patients choices in their treatment, physicians cannot devolve responsibility for advising on what she or he thinks might be best for a patient. In not proposing what is the best in his or her educated opinion from amongst a series of options would be a derogation of professional responsibility.

There is another point about arrogance, and that is the assumption that no one else can do anything that the physicians do. It is pretty obvious that many health professionals can do many of the things that physicians do, from offering advice on specific aspects of care to practical clinical procedures, and it would be foolish to suggest otherwise. Of course many health professionals also bring their own particular expertise to patient care. I feel quite unthreatened by the prospect of increasing 'skill mix' and 'team working'. Indeed that must be the way forward. But if you are seeking the unique role of the physician, you will have to look at the breadth and depth of the knowledge which allows physicians to bring an overall perspective to individual patient care and this is achieved only through a lengthy and rigorous training programme. Such are the physicians who are likely to be those in whom patients will place their trust and confidence. If we fail in our knowledge base and if we fail in our ability to communicate in terms that are important to patients, we will certainly lose that trust and confidence. I do not mean here simply an application of what is now termed 'evidence-based medicine'. There is something missing from that phrase although the alternative of 'ignorance-based medicine' does not appeal either. The problem with evidence-based medicine is that it ignores the particulars and the complexities of an individual patient. Sir Theodore Fox said: 'The human race does not need a doctor but human beings do.'

I much prefer the phrase 'evidence-based care' that encompasses rather more of the application of evidence to the complexities of an individual patient and their problems and what he or she wants in terms of physiological and social well-being as much as the physical relief of symptoms. This is not an argument against the use of evidence, heaven forbid. More, that it is in the incorporation of quality-of-life measures that patients recognise and especially the placing of evidence in the perspective of an individual patient.

Well let me finish now by saying I have been on a rather circuitous route to reach this less than momentous conclusion, that we will need more rather than fewer physicians in the future, and that the characteristics that we have

long prized, combining compassion and empathy, on the one hand, with a strong basis in scientific understanding, on the other, will need to be encouraged rather than discouraged. Only in this way will it be possible to meet the needs of an informed but anxious population of patients who need help and support as they seek longer and healthier lives.

Dawson Lecture

This talk was given at St Bartholemew's Medical School in 1998.

After some laudatory remarks about the late Tony Dawson, a distinguished Bart's consultant and a Queen's physician, I said:

He was a marvellous example of a clinician–scientist and the question I now wish to put is whether he was one of the last of the species or is he a model for the future? The title of my talk, 'Threats and opportunities for clinician–scientists' is a reflection of that question.

I would like to tease out the roles that clinician–scientists have to play, examine the conflicts and compatibilities in this dual role and try to convince you that not only is it possible to bring clinical practice and research together in one person it is absolutely vital for the future health of our population and that we should do everything in our power to foster this critical group of individuals.

One of the major attractions of a career in medicine is the intellectual challenge it presents: the desire to solve problems while at the same time it provides this marvellous bonus of the opportunity to do good for someone, our patients, who by and large tend to be grateful. It's a unique combination and despite the troubles and woes so constantly paraded by a disillusioned profession, continues to attract the most able and bright young men and women into it. And these are just those individuals blessed, or cursed, with an enquiring mind such that they are rarely satisfied with the status quo and are constantly striving to do better. So it should not be surprising that amongst these bright young things there will be a sub-set who are impatient to search out new knowledge and who are, therefore, pre-determined clinician–scientists. Providing, of course, that they are not diverted by the barriers placed in their way. They are an invaluable resource that we must not squander.

There are those who say that the country does not need such high achievers in medicine. We could manage very well, indeed better, with a group of

young men and women whose major attributes are that they are caring and compassionate individuals and, the argument goes, *instead* of high academic achievers let us have kind, considerate doctors. As if care and compassion were the prerogative of the less bright. High intellect somehow bars you from compassion, even though admittedly it does come in handy if you want an accurate diagnosis made and your problem sorted out. Unfortunately recourse to logic does not always convince the illogical, but let us suppose that rationality wins the day and that we can continue to strive for excellence in medicine and in those we aim to attract into it, it follows that we will always have amongst them cohorts of individuals primed to push back the frontiers as clinician–scientists and who will be frustrated if they cannot do so.

Is it worth our while pressing on with this model of clinician–scientist? If research needs doing in medicine why don't we leave it to the professionals – the pure scientists – and leave medical practice to the clinicians? Is it possible to do both well? Even so distinguished a physician as Thomas Sydenham in the 17th century was scathing of clinicians trying to be scientists and urged physicians to stick to bedside clinical observation and care at which he himself was so strikingly successful. And it has to be said that his rather scathing anti-academic attitude has not entirely disappeared amongst clinicians today.

One has to admit that active clinicians have certain characteristics that make them somewhat suspect researchers. So much of practice is empirical and we do have a tendency to rationalize our empiricism. Furthermore we try to exude an air of confidence and certainty so that our patients gain some confidence that we know what we are doing. Scientists, on the other hand, have to have a certain humility, be unbiased and not reach conclusions in advance of the evidence. It is possible for doctors to control their baser instincts but it does require special effort, particularly if we are to avoid the criticisms levelled against us by the basic scientists who do not have the same imperative as we do to get useful results.

This little personality defect we have is, however, a minor difficulty and there is a much keener interest in other factors contributing to the current so-called crisis in academic medicine. The House of Lords Select Committee reported a year or so ago on the grave problems facing those engaged in clinical research;¹ the Richards report examined the nature of the difficulties in great depth and came up with a very long list of recommendations;² and the CVCP has produced a sober response. Yet one does just get a sense of *déjà vu* about this. I will not belittle our current problems but there is an article in *The Lancet* in 1970 by Stan Peart (professor of medicine at

St Mary's) entitled 'The death of the professor of medicine',³ in which he expressed the view that the generic professor of medicine had had his day. He did recant a few years later, in 1983, when he wrote another article for *The Lancet* entitled 'Rebirth of the professor of medicine',⁴ but this episode is an indication that talk of the unsure foundations of clinical science is not new. The formation of the 1942 Club in, I think it must have been 1942, and made up of clinical professors was mainly a direct response to the perceived threats to clinical science and clinical researchers.

So against this background, the recent spate of anxieties should be seen to be part of a rather long running saga and one that has been the backdrop to clinical science throughout my own 30 or more years in the game.

It is not only in the UK where anxieties have been expressed. In the USA, where you might think that clinical science was in a healthy state, successive presidents of the Society for Clinical Investigation have bemoaned the fate of clinical science. None of this is meant to belittle the current problems but rather to say that we have not yet been very successful, despite this long history, in overcoming them.

Why then do we need clinical scientists, what are the obstacles to their activities and how might we overcome them?

The vital role played by clinical scientists has been well rehearsed. It includes, firstly, the understanding clinicians can bring of clinical problems that need researching; secondly, ideas about how such problems can be tackled and what methods might be most suitable, especially if they involve patients directly in the research; thirdly, they can use their clinical experience of the ways in which diseases manifest themselves to illuminate their research; fourthly, they have the ability to conduct research in people, they can explain it to patients, obtain ethical and informed consent and they have the clinical skills and knowledge to undertake it safely. We also have this cohort of bright, effective doctors with their enquiring minds and keen interest in pursuing worthwhile research.

The history of advances in medicine is littered with the successes of clinicians who did research using clinical observation of their patients to enormous effect. From James Lind feeding lemons to prevent scurvy in his crew and Jenner's discovery of vaccination against smallpox to the cause and treatment of coeliac disease and, more recently, the discovery of the bacterium, *Helicobacter pylori*, as a cause of peptic ulcer disease – all major advances based on clinical investigation. On the technological front too we have the application of ultrasonics, of fibreoptics, of angioplasty as major advances. The hepatitis virus story was largely led by clinician–scientists: the clinical trial as a research tool and the way in which immunology has been so

strongly promoted in relation to the needs of transplantation. I could go on and talk about renal dialysis and artificial hips and knees but I think the case for the clinician–scientist is readily made.

However, there has been a huge switch in the emphasis of clinical research and the reductionist approach has taken us to the cellular and molecular level in the study of disease. The molecular genetics revolution naturally involves many clinical scientists but it is increasingly being led by pure scientists. But just as 300 years ago a knowledge of anatomy failed to provide us with an ability to treat most diseases and just as the discovery of the tubercle bacillus had to wait 60 or more years for the discovery of streptomycin, so knowledge of the molecular biology of disease requires an understanding of how it fits into the whole organism in its environment. Sir James Black, when asked where does he think the future of medical science lies, said ‘The progressive triumph of physiology over molecular biology’.

I think he is correct and there is a growing need for scientists who can integrate the discoveries of molecular biology into whole animals in their environment and human ‘integrative physiologists’ are, of course, our clinical scientists.

But there are constraints on clinician scientists. Externally there is the suspicion and loss of faith by the public about medical science and medical scientists. Despite the tremendous advances in medical practice that has been transformed even during my life-time, the public seems less satisfied. We have driven up expectations but have failed to deliver, or so it may be perceived, despite the major advances that have in truth been made. Concerns are expressed by some that high-tech medicine has had little impact on prevention or cure of the major killers and all we do is patch people up. Yet we know that the genetic revolution has the potential to yield enormous dividends. You only have to listen to John Bell in Oxford illuminating the bright new world or hear Richard Sykes at GSK describe, with that shining light in his eyes, the potential for the pharmaceutical triumph over disease, to be convinced that something wonderful lies just over the horizon. But no one seems quite sure when we will reach this nirvana. David Weatherall, in his book *Science and the quiet art*,⁵ puts a realistic, some would say pessimistic, gloss on the time scale over which these marvellous developments will yield practical dividends for the common killer diseases. I share his view that we will see slow incremental progress, but don’t hold your breath.

[Note that this was written in 1998 and there have clearly been many striking advances in cell and molecular biology since then with some obvious advances

in diagnosis and treatment. Much remains to be done, however, before we realise the full potential of molecular biology.]

There is another area where public understanding leaves something to be desired. The potential to misunderstand the nature of scientific advances is too common and a retreat into ill-informed and irrational fears is too prevalent. Two recent examples are the immediate reactions to the news about the cloning of Dolly the sheep – the very word ‘cloning’ has fearful connotations – and the genetic engineering of a number of food crops. Both important for their potential to improve the health and well-being of society but raising all sorts of fears and anxieties, including some that are not entirely rational.

So to summarize this first problem – the public’s attitude to science and scientists.

Their suspicion and, sometimes, their antagonism arises because of the types of experiments we do, because they seem to be self-serving rather than for patient benefit, because they are expensive and because they may seem to de-humanize us. Equally importantly we do not appear to be delivering the promised goods at the pace people want.

We ignore the public view to our peril and it is vital for the future of our discipline that we take on the job of enhancing the public’s understanding of medical science.

The second sort of threat is closer to home and it arises from the drive to efficiency and value for money in the university sector. Desirable aims of course but the question is how they can best be achieved. The reaction of some medical schools seems to have been an exercise in self-immolation. The emphasis on results measured largely in major research council grants and on publication in the highest impact journals had suggested that we might do better if, instead of investing in clinical lecturers, we could put our money in to non-clinical academic staff. The argument goes that you can get much more research out of a basic science lecturer than you can out of a busy, distracted, clinical lecturer doing research in any time he can spare from seeing his patients and gaining his training certificate. Furthermore basic scientists are cheaper.

There is some superficial justification for that view but there is no evidence that non-clinical lecturers are more productive than their clinical counterparts. Indeed I would not be surprised if the reverse was the case. However, that has been the perception and there has been a tendency amongst some medical school deans to pursue a policy of replacing clinical by non-clinical lecturers, without much thought it seems of the longer-term consequences of such a policy. Where, one might ask, are we to obtain our

supply of career clinical scientists, of professors and senior lecturers if we deplete the pool of clinical lecturers even more? The universities, and those same deans, are bemoaning the fact that it is increasingly difficult to find high-quality leading clinical academics to fill their career posts. Needless to say I believe that this is a self-defeating policy and should be resisted.

The research assessment exercise [RAE] has focused resources on the most research active and successful universities. It aims to reward those medical schools judged to be more research active and punish those that are less so. But the implications of that policy could mean that some will become 'teaching-only' schools and we then have to ask whether we can afford to have non-researching schools? If you believe that in order to educate a future generation of doctors you have to instil in them a spirit of enquiry and the need not only to be able to constantly change practice with new knowledge but also to lead that change, then you must have teachers imbued with the ethos of research. Future doctors must be able to explore and develop new ideas and it follows that they should be taught by those at the forefront, at the cutting edge, of their disciplines and that inevitably means that they should be engaged in research. I believe we can ill afford to have any of our medical schools denied the possibility of engaging in research. Who would want to work there?

In reality I do not know of any school that is not active in research at a national standard in at least some disciplines but there is undoubtedly a danger that some will become increasingly unattractive to staff and students.

I also believe that our RAE grades are not a true reflection of our standing in the medical arena. My reason for thinking this is borne out by my experience recently when I was involved in a Wellcome Trust initiative to fund a number of clinical research facilities (CRFs) around the country. Bids were received from over 30 institutions, including all the medical schools, for these large grants to set up a CRF. A team of distinguished American medical scientists were recruited to assess the bids and I was one of two Brits asked to join them. We spent several days in each of the six short listed schools and two things stand out from this exercise. Firstly the Americans were clearly impressed by the high quality of the research in the institutions we visited and had difficulty in excluding any of them. Secondly the five medical schools that were successful bore little relationship to their ranking in the RAE. It did make me think that the RAE assessments, all made on submitted papers, may not be the best way to make such judgements.

There is another paradox in the mismatch between the lack of good clinical academics to fill career grade posts, senior lectureships and professorships, and the sense by those in the training grades that there are few career

openings available to them. It seems that there are opportunities for the most gifted and able but it is a brave young man or woman who recognizes that they have the necessary gifts at the beginning of their careers and are willing therefore to embark on the long period needed to reach their goals when they could move into a purely clinical career post in a much shorter time. There are opportunities for those willing to take that gamble but it seems that there are fewer gamblers around at the moment. There is room here for better dissemination of clear, accurate, information about what opportunities are available for the budding academic clinician coupled with some mentoring and encouragement. We have not been terribly good at that yet.

[Since that time, valiant, and successful, efforts have been made by the Academy of Medical Sciences to fill that gap.]

Much was made in the Richards report² about the way in which clinical service work always intrudes on research time and the need for the academics to complete their clinical training and obtain their training certificates. These factors do little to enhance the attractiveness of the clinician–scientist ladder, and the added pressures of the inflexibilities in training programmes do not help.

Despite these seemingly insurmountable problems it is of interest to read the responses of a large number of young clinical researchers to a questionnaire put to them for the Richards report. One of the things that did not bother them was the prospect of having to spend a longer time in training both clinically and in research. Nor were they concerned about the problem of pay parity with their purely clinical colleagues. Furthermore a breakdown of the hours they spent in clinical and research efforts revealed that they were still able to spend the majority of their time in research. On average they spent 50 per cent of their time on research and 37 per cent on clinical work. None of this suggests that they are not hard pressed and their total hours of work are high by any standard, but it does seem that, given just a little more time and just a little less clinical responsibility, the dividends in terms of job satisfaction and improved morale might be considerable. There are large potential gains from relatively modest organizational change to be had here.

There is another difficulty posed for women wishing to enter an academic career. The extra time involved together with a desire by many to take time out to raise a family and perhaps to work part time are considerable disadvantages. There is more work to do here too.

Against the background I have described of a multitude of threats including a suspicious and unsatisfied public, an unhelpful university selectivity system, a lack of career opportunities, the pressures of service work and inflexible clinical training programmes it is a wonder why anyone would want to go into a clinical research career.

The fact that many do may be because, as Sam Goldwyn said of Wagner's music, 'It's not as bad as it sounds!'

For example, while university funding is constrained, research grant money is rising quite rapidly. Between 1990 and 1997 the Wellcome Trust increased its grants from £70m p.a. to £300m p.a. That is the most dramatic change but they were not alone. The research charity sector as a whole grew from £270m to £420m [note added in 2014: funding by member charities of the Association of Medical Research Charities or AMRC had reached £1.2 billion) and even the government-funded MRC [Medical Research Council] more than kept pace with inflation with grants rising from £250m to £309m, a rise of some 24 per cent. The funding from commercial sources also rose, sometimes quite markedly, for contract research and at the same time research and development moneys from the NHS R&D division have seen a rise.

So something is happening and the money must be going somewhere. It is going into the 900 or so medical research fellowships of one sort or another and funded by the MRC and the AMRC and there are probably 100 more supported from other sources.

So that's part of the input. It is not so easy to measure the output. Certainly the number of research publications is rising exponentially each year. Although citation indices may not give a clear picture of the quality of these outputs, Robert May, government chief scientist [author's note: later president of the Royal Society and later still, elevated to a peerage] in his analysis of outputs concluded that the UK was more than holding its own in medical research.⁶ In fact the UK was first or second on a number of measures in an international comparison table that included the USA and Japan. If one goes to international meetings in any medical specialty it is hard not to be impressed by the extent and quality of the UK's contribution. The American panel enlisted to assess the bids for Wellcome CRFs was clearly impressed in any case.

So this is not to say that there are few problems for the clinical-researcher, clearly there are, but it would be equally wrong to belittle what is being achieved or to ignore the opportunities that are opening up. We will not be seen to be credible if we concentrate solely on how badly we are being treated and how impossible it is to carry out research. That is not only an inaccurate

reflection of what is being achieved it also perpetuates a sense of frustration and spreads a demoralizing influence on the young. It is much easier to spread discontent than content and it is very counterproductive.

There are indeed a number of opportunities available to us.

Firstly, influencing public opinion. Educating the public, enhancing their understanding and helping them grasp what research is capable of and what it cannot do. There is an organization called COPUS – the Committee on the Public Understanding of Science – on which I happen to be the token medic, and, while it has had some modest success on the broader scientific front, it has had no impact in the medical science arena. I felt that we needed a body that focused on the public understanding of the medical sciences. I suppose I should have learnt by now but, because I had been pressing for such a body, I found myself chairing something called COPUSIM, that is COPUS in medicine. It will begin work in September and I hope it might form a focus for this sort of activity.

[Note: this unattractively named organisation only lasted a year or two but subsequently a number of other bodies have taken up the cudgels, especially, Sense About Science and the Science Media Centre which have been very successful.]

There are a number of other opportunities for us too. Medical research is certainly going through an exciting and stimulating time, making it an attractive option for young enquiring minds. But while it has been easy to make recommendations for change it has been, as always, in their implementation where the difficulties lie. There are a number of ways in which improvements might be made. Firstly, a longer-term change worth pursuing is the idea of university hospitals. An idea that has been around for some time and emerges again in the Richards report. It requires hospital trusts and universities to come together as single entities, funded as one and under one management. It is a pattern seen in some large American hospitals and to an extent at the Hammersmith Hospital. Although it may not work everywhere it would help ensure that service, teaching and research were seen as an integrated whole and get round the ‘us’ and ‘them’ attitudes. It would also remove the need for complex contractual arrangements between trust and university. [In 2014 it remains a desirable, but as yet unachieved, ambition.]

Then we should convince the Higher Education Funding Council, England (HEFCE), and in particular our colleagues who sit on the RAE panels, of the implications of their deliberations. While still supporting excellence they must be more sensitive to the need to reward excellence even

where it exists as islands in a medical school with an otherwise more modest overall output. A blunderbuss approach is unhelpful and they should not be eager to mark down the medical disciplines in comparison with non-medical subjects.

As far as efforts to reduce the service load on young researchers is concerned some relief has been gained in those departments where they have been able to build up a critical mass of clinical scientists. This has sometimes been achieved by external funding but more often by the merging of departments with common interests. We have been rather too fond of developing small fiefdoms in our own disciplines and this is very unhelpful to those working in these departments. There is no doubt that with a sufficiently large critical mass it is possible to develop flexible rotas of service commitments, leaving sufficient freedom to pursue research.

Then there are the thorny issues for the young of job opportunities, job security, obtaining training posts and the perceived impotence of the academic community to influence those thought to be responsible for their problems – the postgraduate deans, the colleges, the Specialist Training Authority and the Department of Health's manpower planners.

I believe we can help dispel some of these anxieties if we gather and spread full information about where there are opportunities, where the flexibilities, that do exist, lie and guiding the young in the right direction. There is a great deal of ignorance around and I feel we could be doing more here as a body of academics to become involved. One of the difficulties, of course, is the lack of a representative body for the academic community. We do not have a voice. [Hang on for the Academy of Medical Sciences to ride to the rescue, formed in 1998 and now, in 2014, an authoritative voice and a very effective organisation.]

We are not short of informal discussion groups, however. We have the 1942 Club, the Academic Medicine Group, the Association of Clinical Professors of Medicine, etc, etc, but none that can reach a decision and put it into action. The Council of Deans of Medical Schools has begun to get its act together but it is under the influence of the vice chancellors and may not always reflect the views of the clinical academic body at large.

There is a vacuum for clinician–scientists and we lack a mechanism for gathering views, formulating proposals and, most importantly, implementing them. We need an authoritative voice and there is now some hope appearing over the horizon. There have been discussions for as long as I can remember about the possible formation of some form of an academy of medicine that would bring together all those in academic medicine and act as a focus, perhaps akin to the American Institutes of Medicine. Well, at last

it looks like we might be getting somewhere. After much debate, and some blood on the carpet, I chair the implementation group for a new Academy of Medical Sciences that is about to be born. It was agreed by its parent bodies, the Council of Deans of Medical Schools, the colleges, the postgraduate deans and the Royal Society, and they have each selected their founder members, about 350 of them. A grant from the Wellcome Trust has secured accommodation in Carlton House Terrace alongside the Royal Society and the founder members are busily electing the council and officers. The first meeting is to be held on July 7th and it is hoped that the Academy will be up and running by October.

This is obviously an exciting development and much will be riding on its success. I am hopeful that it will be able to take up many of the issues I have been describing. Much is expected of it but if it works as intended then we will see benefits that have long been needed.

So, in finishing, I hope I have been able to give you a picture of the problems faced by clinician–scientists and why there is a clear need for them to be overcome. But I hope too that I have convinced you that we are in a rather better position now to ensure the future of this vital group of men and women.

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Abstract of Croonian Lecture

This lecture was delivered at the Royal College of Physicians in 1990.

My purpose in this lecture was to describe some of the research, in which my co-workers and I had been engaged, into the control of absorption and secretion of salt and water in the small intestine. You might think that this was not a topic that would stimulate much excitement outside a small group of oddballs with peculiar tastes. Until, that is, one's mind is taken by the striking example of cholera where patients may lose 20 or more litres of salt and water through their intestinal mucosa, and begins to question how it might be possible for the intestine to change so dramatically from an absorbing organ into a secreting one.

What follows is brief outline of that lecture written in as lay terms as I can manage given the technical nature of the subject.

The human intestine has to cope with huge amounts of fluid entering it every day. About 2 litres per day enter in food and drink but the majority of the 7 or more litres with which it has to deal arrives from the digestive secretions of the stomach, pancreas and liver. Of this large volume only about 200 mL is allowed to escape in the stool.

Trying to understand how the intestine achieves this is where I had been spending much of my time for the previous 25 years.

It had become clear that the small intestine, with its millions of minute finger-like villi that protrude into the lumen, was not only absorbing fluid but, at the same time, it was secreting fluid in a peculiar balanced circuit. It was this secretory process that was switched into overdrive in cholera and a number of other severe diarrhoeal diseases. The loss of such enormous volumes of fluid in cholera causes the severe, often fatal, dehydration that characterises the condition. But the most surprising feature of the disease is the fact that the lining of the gut looks perfectly normal under the microscope. There is no inflammation or structural damage. The disease seems to be working entirely by the turning on of a switch at the biochemical level.

Furthermore, the ability of the intestine to absorb salt and water normally at the same time is remarkably preserved and has led to the practical use of oral rehydration therapy that has so dramatically reduced the mortality rate.

So the question we were interested in solving was: How is it possible for the intestine to absorb and secrete fluid at such a rate and at the same time? It had long been assumed that absorption occurred through the villi and secretion through the crypts lying deep between the villi. The surprising answer came, however, when we investigated the structure of the intestine using micro-puncture techniques.

Under a high-powered microscope we inserted minute electrodes into cells on the surface of intestinal villi and into some cells based in the crypts between the villi. When we stimulated the gut to absorb we found that it was the villi that did the absorbing but, when we stimulated secretion, it was both the crypts and the villi that responded. So here we had the structural basis of a balanced fluid circuit in crypt and villus showing that the two processes could go on at the same time and probably through the same cells.

Later we were able to confirm that the driving force for fluid secretion was the active extrusion of chloride ions across the apical membrane of isolated epithelial cells.

It is possible to isolate the outer membrane of surface epithelial cells lining the gut and when you do that the membranes curl up to form spherical structures, vesicles. Using this technique we were able to demonstrate directly the presence of the channels through which chloride ions pass. We also found an ion exchanger in which chloride ions exchanged across the membrane for bicarbonate ions. This was interesting in that it showed one way in which bicarbonate might be secreted into the lumen of the intestine, an important alkalisation of intestinal contents, as chloride is absorbed. It also confirmed something we had shown in John Fordtran's laboratory in 1968 when we suggested that a chloride/bicarbonate exchanger existed in human small intestine using perfusion techniques in human volunteers.

It had been known for some time that the toxin of cholera stimulated a biochemical response that led to secretion and that the intermediary that was switched on in epithelial cells, the so-called 'second messenger', was adenylyl cyclase. This in turn liberated cyclic AMP (adenosine monophosphate), which then caused the secretion of chloride ions.

Geoff Sandle, our micro-puncture guru, showed very nicely that the reason chloride ions were being secreted was because the channels or pores through which they pass across the cell membrane open and close at a much greater rate than in the resting state. They remain open for a fraction of a second but it is the frequency with which they open and close that increases

when secretion is activated. He was able to demonstrate this in isolated, minute patches of epithelial cell membranes in which only one or two ion channels exist. This sophisticated, 'patch clamp' technique has been used in many studies of ion channels in nerve cells to study neural transmission, but rarely in the intestine.

We were very interested in how net absorption, that is the balance between absorption and secretion, was controlled. We knew that absorption of salt and water was stimulated by the digested products of foods, such as sugars and amino acids. We also knew that a number of neuropeptides influenced secretion. Using isolated pieces of epithelium from the rat intestine, stripped of its muscle layers, and mounted in special, Ussing, chambers, we could control the composition of the fluid bathing each side of the mucosa. We were then able to measure the flow of radiolabelled isotopes of sodium and chloride from one side to the other under strictly controlled conditions. For example, we could demonstrate stimulation of secretion by a whole host of agents, including prostaglandins and cholinergic neuropeptides, and inhibition of secretion by opiates.

It had become clear that cAMP was not the only pathway by which cells were stimulated to secrete. Inside all living cells the concentration of calcium is maintained at a very low concentration and much lower than the concentration in the plasma bathing cells on the outside. An active process of extrusion is at work here. Even a very slight increase in intracellular calcium concentration triggers secretion. We were interested to explore how calcium did this and found that, while calcium influences a host of intracellular processes, so far as secretion is concerned its effect on a particular lipid in the cell membrane, inositol trisphosphate, was the key. This route involves the phosphorylation of the relevant transport protein in the cell membrane causing a change in its shape and conformation. It turns out that the neurotransmitter acetylcholine, which is a strong stimulant of secretion, acts through at least two such calcium-dependent pathways. Furthermore as the calcium-dependent enzymes split the membrane lipid, two fractions are liberated, one of which stimulates secretion while the other curtails the extent of secretion acting as a brake on over-secretion.

In summary, then, we found that there are several external stimuli to intestinal secretion, including neurotransmitters (hinting at a nervous control of intestinal secretion), and substances liberated in any inflammatory reaction, inflammatory mediators (suggesting a mechanism underlying diarrhoeal responses to intestinal infections). There were also several intracellular mechanisms by which these extracellular stimuli were converted into a secretory response.

But what did all these *in vitro* demonstrations mean for normal living physiology? As is so common with the *in vitro*, reductionist approach any effects that are demonstrated in isolated cells or tissues may have little to do with the situation for whole animals or man. It was important therefore for us to try to see if we could find evidence of similar neural effects in whole humans. We studied human volunteers, that is bribed medical students, whom we induced to swallow tubes that could be passed on into the small intestine. Using the technique I had learned in Dallas with John Fordtran we infused saline into the top of a segment of intestine and aspirated samples from the bottom and could thereby measure how much had been absorbed or secreted. That at least, was the principle, although it was somewhat more complicated than that. But using this technique we showed that blocking the parasympathetic nervous system, with intravenous atropine, caused an increase in absorption. Furthermore mimicking the effects of parasympathetic stimulation with neostigmine induced secretion. These observations suggested that the parasympathetic, cholinergic nervous supply to the gut was maintaining the normal secretory part of the balance between absorption and secretion. Finally, when we mimicked the effect of the sympathetic nervous system on absorption we showed that sympathetic agonists stimulated absorption and a sympathetic blocker (propranolol) inhibited absorption. So here was some evidence that the autonomic nervous supply to the gut might control absorption and secretion.

But do these observations have any physiological significance? To try to tease this out further we studied another cohort of volunteers but this time we measured the effects of psychological stress on intestinal absorption. Stress was induced by a technique used by psychologists in which two different stories are relayed through ear phones, one in each ear, and every so often a question is asked in one ear about the story being read into the other – all at the same time as we perfused their intestine.

That this is stressful was confirmed by the rise in pulse rate and blood pressure that these manoeuvres produced. In the control period only one story was read into both ears and pulse rate and blood pressure were unaffected. It was easy to show that this type of stress caused a fall in absorption from the small intestine and this observation was repeated when we measured the effects of pain on absorption.

We were also able to show that sham feeding, that is chewing a meal but not swallowing it, causes the stomach to secrete acid, a well-known response, and it is also known that this effect is mediated through the vagus nerve, the major route for the parasympathetic supply to the intestinal tract. We showed that sham feeding also inhibited absorption or stimulated secretion in the small intestine.

Taken together all these observations allowed us to postulate that under normal conditions there was a sympathetic and parasympathetic tone that controlled net absorption of fluid. In other words, the autonomic nervous system was capable of influencing fluid absorption.

Transport of salt and water across the epithelial lining of the intestine is clearly a vital process that is essential for normal life. It is not surprising therefore that a complex set of regulatory processes have been developed to control it. There is no doubt that the major drive to normal salt and water absorption is the presence of nutrients in the intestinal contents. But there are many other factors that can influence the rate and extent of net absorption, not least of which is the activity of the autonomic nervous supply to the intestine. Other hormonal influences also play a part and probably affect net absorption too. In addition, the presence of any inflammatory process, perhaps the result of an infection, causes a number of inflammatory mediators to be liberated locally and they too can influence the balance between absorption and secretion. A number of diarrhoeal diseases, of which cholera is the most extreme example, occur when the secretory drive dominates over-absorptive processes.

At the cellular level the transmission of all these external stimuli is dependent on a number of different second messengers that transfer the message from outside the cell to the inside. Internally a series of biochemical steps take the secretory message on to its final common path in the ion channels sited in the cell membranes, which in turn respond by opening at an increased rate.

At the end of my talk I pointed out that much of this work was carried out by a team of researchers and fellows coming through the department over a number of years. I was fortunate to be able to work with them.

Jewish medical ethics

This lecture was given to the Maimonides Foundation in 2003.

Let me say at the outset that while I am certainly Jewish and I have been a practising doctor and while I have taken an interest in medical ethics, I cannot claim to be an expert, much less an authority. So what I say cannot be taken as gospel, if you will forgive the expression. My views are those more of an interested observer.

I will focus on end-of-life issues, where ethical concerns are most acute; when life begins in the womb and where it ends in the grave. These two extremes have certainly taxed us in the Lords in recent debates. The debates on embryonic stem cells and cloning at one end and on assisted suicide at the other have been striking examples.

It is interesting that the rabbinic authorities have some very clear-cut responses to such matters and that these arise out of a number of basic principles. And what is most surprising is the fact that despite the seeming severity and rigidity of Jewish law, with the strict discipline it demands of orthodox Jews, it is remarkably flexible, tolerant and pragmatic when it comes to health and medical care. This is because it relies heavily on its use of a very small number of underlying principles that are firmly based on interpretation of the Bible. It is the Bible that determines the Jewish ethical position against which any new medical or technological advances are judged. Much like English common law, new judgements are made on a case-by-case basis but on each occasion referral is made to the Bible which is regarded as the font of all ethical judgements.

So how does all this play out in practice? Well firstly Jews do not believe, as do some groups, that illness is God's will and therefore we should do nothing to intervene on the grounds that, if it is God's will, he will also find a cure. Instead, the Jewish ethical position is that we should use God's gifts of wisdom and understanding to relieve suffering and save life. And because this is a divine licence it is also an obligation and ethical requirement.

It probably explains why so many rabbis through the ages were also physicians, including, of course, Maimonides.

The second basic principle is that of respect for the dead that is placed very highly. Desecration of the dead is viewed badly and it is why post-mortem examinations are so contentious. But there is another basic principle that trumps respect for the dead and takes precedence over it, and that is the sanctity of life and by extension the saving of life. To save a life it is permissible to do almost anything except, interestingly, commit murder, adultery or idolatry. Everything else is acceptable.

For example, doctors can work on the Sabbath, drive a car, use machinery to tend to the sick and dying, while none of this is allowed under normal circumstances. It also allows patients to take forbidden foods if it is essential; for example insulin derived from a pig or a pig heart valve transplant. Anything to save a life is not only permissible it is obligatory – the moral duty to tend to the sick.

These basic principles have allowed the rabbis and rabbinical courts to make judgements on most if not all the new developments in technology that are stretching the boundaries for ethical debate and creating new dilemmas

This plays out in end-of-life issues and the one that received a lot of attention recently was research using human embryos and stem cells. The Jewish ethical position is surprisingly clear cut, and not in the way one might imagine. Dayan Ehrentrau, the head of the Jewish rabbinic court, gave a very clear exposition of the orthodox Jewish view when he gave evidence to the House of Lords Select Committee. He said that where human embryos are already created for IVF [in vitro fertilisation] treatment of infertile couples then the spare embryos, that is those not to be implanted in the womb and which would otherwise be discarded, could be used for the research envisaged in the bill being discussed at the time. The bill proposed that research on human embryos should be extended, from simply that which was necessary to understand and treat infertility or to detect congenital abnormalities, to research with stem cells derived from these embryos that would lead to potential new treatments for severe diseases such as Parkinson's, diabetes and so on. Ehrentrau said that that was entirely acceptable provided that it was done on discarded embryos after IVF treatment and that embryos were not created simply to carry out research. Furthermore the use of such stem cells in therapeutic cloning was also allowable because of the lead they could provide for new treatments, although not for reproductive cloning. All that fits in with the concept that it is a divine responsibility to use our ingenuity to save lives. Saving lives takes precedence over a natural repugnance to

experiments on human embryos. All of that was supportive of the bill that eventually passed into legislation.

This type of reasoning has long been used in other onset-of-life issues: contraception and abortion, for example. These are unacceptable in any religion such as Judaism that values life so highly, but even here there may be overriding ethical principles that render them permissible in certain circumstances. For example, contraception, preferably with the pill, is acceptable if the life of the mother would be endangered if she were to become pregnant. The life of the mother, an existing person, is deemed higher than the life of a potential but not yet existing person and this is taken even further in the case of abortion. Again if the mother's life is endangered by the pregnancy then an abortion becomes allowable, and here we have to look at how the embryo, fetus and unborn child are regarded. There is no doubt that from the moment of conception we have a potential human being that slowly develops and that should, therefore, be treated with respect, care and attention. Rabbis surprisingly do not seem to get bogged down in trying to determine when life begins as many did in our debate in the House of Lords. Does life begin at the moment of conception? Is it at the 14-day stage when the first signs of the primitive nervous system become clear? Or at any other time? The rabbis do not debate this endlessly as they do most other things because, although the unborn child is undoubtedly a potential person, it is not regarded as a person until it is born. Now this is a remarkable position to adopt but it is based on a number of biblical sources that lead to a number of conclusions. Firstly an aggressor who attacks a mother, and her baby *in utero* dies, is certainly guilty of assault but not murder. If he kills the mother he is clearly a murderer. If the fetus *in utero* is a threat to the mother's health than an abortion becomes permissible. One authority suggested that the fetus could be regarded as an assailant out to harm the mother. The principle remains the same: the life of the mother is to be put above that of the unborn child who is not yet regarded as a person even though they should receive every protection possible apart from when they threaten their mother's life.

So far as IVF for infertile couples is concerned Jewish law has no major problems. Anything that allows an infertile couple to have children, which is itself held to be a divine objective, is strongly supported. Where problems do arise, however, is if the sperm and the egg used in the test tube are not derived from a husband and wife. That then becomes a much more complex issue and by and large it is not allowable. Questions of whether it would constitute adultery come in to it and the whole thing becomes somewhat messy.

It is clear that there is a strong sense of the sanctity of human life running through all these issues and this has been applied, in a variety of ways, to each of these knotty problems.

When we come to the other end of life, similar concerns about the sanctity of life permeate Jewish medical ethics. This colours our view of people who are seriously ill and coming to the end of their lives and, while it is not only permissible to relieve their pain and suffering, indeed it is mandatory, it is not allowable to shorten the life of such a person. The orthodox view is that it is God who gives life and who takes it away and it is not in man's gift. Inevitably this means that euthanasia and assisted suicide are both outside Jewish law and ethics. It also means that, while useless or harmful treatments have to be avoided, treatments which are effective should continue to be given until the person dies. This is quite a tricky one and makes 'do not resuscitate' orders difficult to call even for hopeless, terminal cases.

Once a person is dead we come to the controversial issue of postmortem examination. Respect for the dead is a dominant theme so postmortems are frowned upon. The rabbinic court in Israel, however, agreed that blood specimens and biopsies taken after death were acceptable for diagnostic and research purposes. This was based on a biblical measure of what constituted the smallest thing for which a person has to have concerns and that turns out to be the size of an olive! Anything smaller than an olive – a biopsy, a tissue block or microscopic slide, for example – can be retained and does not have to be buried with the body. This seems to me to be an entirely pragmatic approach and it allowed, for example, pathology departments around the country to retain all their tissue blocks and slides taken from Jewish patients and not to have to return them for burial. The recent flurry of interest in pathology specimens is straightforwardly resolved for the orthodox by recourse to the olive.

Judging the moment of death poses difficulties too because this is dependent not so much on such things as brain death or even brainstem death but on complete cessation of both respiration and heartbeat. This makes for problems for organ transplantation because, while organ transplantation is quite permissible, it fits in quite logically with the need to do everything possible to save a life, it means that some organs may not be viable for transplantation. Corneas and kidneys may be possible but livers and especially hearts will not be in a good condition. So that can be tough and certainly limits the availability of some organs. I gather that in the last year or so the rabbinic court in Israel has taken a slightly more lenient attitude and allowed brainstem death, which it is now possible to diagnose with more certainty, to be included in the definition of death. That clearly

makes heart transplantation more feasible but it has to be said that this is a controversial definition of death and it is not yet accepted by UK rabbinic authorities.

These are just some of the end-of-life issues that pose ethical dilemmas for Jews. Although all of these medical ethics are based on biblical sources they do seem to be adaptable in most instances to modern technological developments.