The Academy of Medical Sciences

The Academy of Medical Sciences 10 1998-2008 Research at the heart of health

Presidential perspectives

Professor Sir John Bell talks to Geoff Watts about medical science – from the recent past to the near future

As part of the Academy of Medical Sciences' 10th anniversary celebrations, we asked Dr Geoff Watts FMedSci to conduct a series of interviews with the President, Professor Sir John Bell FRS PMedSci. The broad theme was 'medical science, from the recent past to the near future'. Captured here are some highlights from the interviews, giving Sir John's perspectives on molecular medicine, stem cells and diseases of the developed and developing world, as well as the role of the Academy.

Molecular medicine

'The rapid advances in human molecular genetics seen over the past five years indicate that within the next decade genetic testing will be used widely for predictive testing in healthy people and for diagnosis and management of patients.' – John Bell. BMJ (1998) 316, 618.

Making predictions on the record is risky - but Professor Sir John Bell has the self-assurance to offer an occasional hostage to fortune. As the date on the quote above from the BMJ reveals, not every prediction hits all the bull's-eyes dead centre. So does he now recoil from his 1998 vision of the future of molecular genetics? Not at all; his confidence in the science and its relevance to clinical medicine is undiminished.

'I got the time frame wrong. But I think most people would now accept that this [the impact of molecular genetics] is real – and will become more real. It's very difficult to see how we can continue the same paradigm of health care with its dramatically rising costs and the relatively inefficient application of costly new therapies across large populations when they give only modest benefits. In fact we know that if you can find the population in which those therapies work really well, efficacy rises dramatically.'

The Presidency of the Academy of Medical Sciences is an office carrying many obligations including, inevitably, an expectation that its holder will have informed opinions on everything. This is hardly possible; but two hours of wide-ranging discussion suggest that Bell knows what he thinks about the past developments that have shaped the medicine we have today, and about the current research which is even now creating its future. His own principal research interests lie within one of the topics set to change the way medicine operates: the molecular basis of disease. So a good place to begin this skim through some of his thinking.

'I think there's a rule that big discoveries in biomedicine take at least 20 years to impact in the clinic.'

That he sees the sequencing of the human genome as a scientific milestone comes as no surprise. But a clinical one as well? 'I think there's a rule that big discoveries in biomedicine take at least 20 years to impact in the clinic. Monoclonal antibodies are an example. They were invented in the early seventies, but the first therapeutic antibodies appeared in the mid-nineties.'

'You have to take the human genome in that context. Genetics and genetic manipulation really emerged in the mid seventies when we learned how to stick two pieces of DNA together. They started to impact on drug discovery and the identification of new targets by the mid to late eighties. But the sequencing of the genome and an understanding of the variation within it only came in the early to mid nineties. We're now beginning to see the first tests having wide applications in diagnostics. But it's an exciting initial step.'

In short, Bell has no doubt that the human genome project will change medicine radically. Recalling his 1998 BMJ article he laughs, 'It's one of my most cited papers because most people hated it. They didn't believe it would happen. The charge was lead by some people in the genetics community who were used to dealing with highly penetrant single gene disorders and

didn't believe we'd ever be able to make sense of the big complex traits.' The idea that cardiologists and oncologists and rheumatologists would all be using these tools to make decisions about their patients was not, it seems, one that roused initial enthusiasm.

One of the doubts sometimes voiced about the personalised medicine made possible by the genome project is that this customised approach will prove prohibitively expensive, with increasing numbers of drugs being produced for ever smaller groups of patients. Bell sees the concern, but reckons that if it does prove to be a problem, it's still a long way off. On the time scale of which he's thinking, clinicians would be using predisposition genes, the expression levels of certain genes, epigenetic markers and a variety of other ways to identify sub-groups of perhaps 10 or 20 per cent of a population of patients with a particular disorder. 'If you take a drug which, in a large randomised trial, gives you efficacy in say only 30 per cent, but you then identify those 30 per cent and treat only them, your efficacy rises dramatically.' And it's good for the pharmaceutical companies. 'They'll penetrate the market much more effectively. In that 30 per cent, everyone's going to want the drug.'

Cost in the longer term, if the 'personalisation' enterprise does make inroads, is hard to judge. But Bell remains optimistic. He quotes the example of people who develop a severe myopathy in response to treatment with statins. One genetic variant accounts for the vast majority of cases. 'The tools to find the genetic variants that cause those rare adverse reactions are increasingly available. Provided it's part of an integrated system in which you pay once for a DNA chip giving you a broad range of information…well, I think that works.'

'The concept of hypothesis-driven biomedical science that's shaped the research agenda has got some holes in it. You've got to be very careful not to be too confident about what you know, because chances are it's wrong!'

Twenty years ago only a handful of known gene variants had been associated with a predisposition to common disease. By the beginning of this year, says Bell, there were 130. By the end of it there will be over 200 and, by the end of next year, 400. 'None of those original 130 would have been on anyone's list of candidate genes that might cause disease. So the concept of hypothesis-driven biomedical science that's shaped the research agenda has got some holes in it. You've got to be very careful not to be too confident about what you know, because chances are it's wrong!'

A wish

Asked to pick just one medical achievement that would give him the greatest satisfaction, he singles out the avoidance of premature death in young middle-aged people. 'Serious disease afflicting anyone aged 35 to 40 is a complete nightmare. It destroys family units and it's disruptive from a societal point of view. Although the numbers are fairly small, the impact is disproportionately great. The deaths are mostly due to vascular disease and cancer.' And there is, of course, no single or simple remedy.

Stem cells

The topic of the moment in biomedicine - at least as measured by the media coverage - is the creation and use of embryonic stem cells. Here too Bell applies his 20 year rule of thumb, but he worries about the distracting effect of arguments between supporters of adult versus embryonic cells. 'The hum and buzz associated with the use of human embryonic cells is understandable, but the opportunities associated with adult stem cells should not be missed. Mesenchymal cells from bone marrow that can be differentiated into cartilage and fibrous tissues for use in orthopaedics look pretty interesting to me. And I think there will be other examples.'

'The fact is we need research across several

arenas - adult (including reprogrammed cells), fetal and embryonic stem cells. The research is complementary – at present, we don't know which route will ultimately be most effective, and closing off any one avenue of research could be detrimental.'

He stresses the importance of ongoing dialogue between scientists, policymakers and the public on stem cells and other issues. 'The Academy's report in 2007 on inter-species embryos was an important platform to explain the science calmly and objectively and to promote consistency around terminology. It is this dialogue that has resulted in a Human Fertilisation and Embryology Bill that commands wide support and that will keep the UK at the forefront of stem cell science.'

On planning research

In planning a programme of future research Bell likes to talk of 'placing bets': of backing what you see as a fruitful direction in which to proceed. He illustrates this by referring to Professor Sir David Weatherall, his Oxford mentor. Weatherall, certain of the imminent emergence of molecular medicine in general, chose to back research on the globinopathies. The bet paid off. When Bell's turn came to pick winners he decided to put his efforts into the genetics of common diseases: a development which, as he'd said in his BMJ article, he believed would transform medicine. Hence, for example, the Wellcome Centre for Human Genetics. 'It's gratifying to see this work now paying out - even if not in quite as short a time frame as I'd predicted.'

Diseases of the developed and developing world

One of the diseases in which Bell takes a close interest is diabetes. Its rising incidence - an increasing cause of concern - is not of course confined to nations where affluence is already well-established. If Hong Kong is the forerunner of what the rest of China can anticipate, says Bell, the scale of the problem that awaits is truly vast. 'There is an opportunity to recognise that this is coming and do something. But this hasn't been properly discussed at a policy level, nationally or internationally, and it's going to create a huge burden for health systems.'

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The policy decisions that need to be taken involve economics, education, changes to the way we live, and much else. 'The World Health Organisation is very good at managing infectious disease problems, but has yet to seize on chronic diseases in a serious way. It spends only about 2-3 per cent of the budget on them. HIV, malaria and diarrhoeal diseases will continue to wreak havoc among the billion poorest people on the planet, but we've also got to keep our eye on this other epidemic of diabetes. This is a health problem that will only be solved by hooked-up thinking across governments.'

We haven't yet learned how to live with affluence; genes selected for times of scarcity now have to function in times of plenty. Many of the actions required to tackle diabetes could, of course, be introduced without a more detailed grasp of its molecular and genetic underpinnings. But to understand these things is still important in Bell's view. Take, for example the role of the beta cells.

'In the eighties and the early nineties, most scientists in North America felt that diabetes was a disease of insulin resistance in the periphery. In Europe the beta cell was seen as more important. As soon as the first genetic variants started to come out, they were all in the beta cell. It's now clear that this cell is central to the disease. So how do you maintain your population of beta cells? And what happens in later life when the beta cells start to get tired? Are there ways of revving it up

again?' All questions that need to be answered. The investigation of diabetes at the molecular genetic level is still a relative novelty; molecular studies of cancer, on the other hand, have been going for decades. Responding to the suggestion that biologists have over-exploited cancer as a handy justification for funding studies in basic cell and molecular biology, he concedes that the charge is not without foundation. 'It has become a sort of catch-all for grant applications which start by quoting the mortality figures for cancer and then drift into a proposal about Dictyostelium.' But at core, he insists, there is a body of knowledge to be garnered that is directly relevant to the disease. 'I am not pessimistic. An understanding of what individual tumours are doing, and which will be good or bad responders to therapy - which genomics is now providing - will be very powerful.'

What hasn't materialised is a silver bullet. 'But when you understand the diversity of genetic and cellular defects in cancer you start to see why there probably won't be a silver bullet. It's another case where we're going to see increasingly personalised therapy. These people have a defect in this particular pathway, so hit them with this agent. Herceptin is an example.'

The technology alas won't be cheap. 'The cost of therapy for cancer is going to be astronomical. What's the value of six months of life for someone with pancreatic cancer?' It's a question that hangs unanswered over many if not most of the new biologics, including those being developed for chronic diseases such as arthritis. In this case, he thinks, the economic case for costly treatment is more easily made. Expensive but early medical treatment should bring later savings on hip and knee replacement surgery and the like. 'But are we prepared to take the money we'd otherwise be spending on these procedures and frontload it?' He's not sure – but heartened by what he see as a greater willingness within the NHS to consider innovation.

It would be wrong to imply that John Bell is bullish about every branch of medicine. He views chronic degenerative disease – neurodegenerative in particular – with trepidation. 'I've got an aged mother. She said that when you get to her age – she's 85 – you don't necessarily want to run a marathon, but you're interested in two things: vision and your ability to think straight. They're fundamental to quality of life. We've made some progress with vision, but not so much with neurodegeneration. The fundamental pathobiology is still uncertain. People with Alzheimer's disease get amyloid; but whether that's what stops them thinking is another question.' There's amyloid in the diabetic pancreas, he points out; but this doesn't causes the disease. As discussed in the Academy's latest report on 'Brain science, addiction and drugs', cognitive enhancers may have something substantial to offer in the future, but much more research is needed.

'It's very difficult to manipulate things in the way you can with lymphocytes or tumours. It's a systems problem in a system that's difficult to get at and even harder to sample. Think of neurogenesis. We never thought nerve cells could regrow. Now we know there are stem cells in the brain. This may be fundamentally important; but it's a recent discovery.'

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To the millions living in poverty in Africa and Asia who would count themselves fortunate to reach even three score years and ten, fears about the quality of life in extreme old age might seem unreal. Which raises the question of whether global medical research is skewed too much towards the preoccupations of the rich. Bell has two observations to make. First, the tradition of 'tropical medicine' established in the UK during the colonial era survived decolonisation. 'We do better than almost anyone else. We punch way above our weight in infectious diseases, TB, dengue fever, HIV and so on.' His second

comment focuses on the convergence between the health problems of the rich worlds and the hitherto poor. Countries like India and China with a rapidly expanding middle class are freeing themselves of infectious disease and have begun to experience the health problems of the affluent. At least one possible future scenario leaves him feeling uneasy. 'In countries like India and China there will, for a period, be a very poor rural population with no access to expensive medical care and a large middle class who can afford this care.' Certain possible responses to this dilemma would be damaging. 'For example, one of the risks is that these countries, trying to ensuring that the new medicines are made available to their populations, will – as Brazil has done in the past – abandon patent protection. This would really disrupt the system and cause severe problems. How you would manage that I don't know.'

UK Biobank

To the minority of clinicians and researchers who still doubt that UK Biobank represents value for money, Bell responds - with characteristic verbal emphasis - that how genes interact with the environment is the BIG question. 'You can't answer it without prospectively collecting good environmental data from large sample sizes that allow you to do the genetics. The UK is the only country in the world in a position to do this. The Americans began and gave up. The Canadians have talked about it, but haven't started. The Scandinavians have too small a population. By the time anyone else gets properly going we'll be ten years ahead. So it was a spectacularly clever investment.'

No-one, of course, can be certain what will come out of Biobank. But the serendipitous nature of the enterprise is, to Bell, one of its strengths. He returns to his concern (see text) about an over-reliance on hypothesis-driven science. 'Don't pretend you always know what questions to ask, because you don't. Of course, these big all-singing all-dancing cohorts aren't going to tell us everything. But they're going to be very important.'

The Academy of Medical Sciences

The issue of global health is one to which Bell would like the Academy to pay more attention in the future. This wish prompts the question of what other developments in the Academy's activities he would like to see during his presidency. He says he envisages no immediate need for a radical change of direction – which would anyway be an odd ambition for a young organisation still successfully ploughing its original furrow. 'But I think we can also do more in terms of mentoring and of capacity building for academic medicine.'

More generally he wants the Academy to keep doing what it already does well: its interaction on policy issues with policy makers and the public. His other ambitions, though no less essential, are also more parochial: to ensure the financial security of the Academy, ideally through a grant in aid or some other steady source of support; and to see it safely into the new premises in Portland Place, London.

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'This will really help to give us an identity,' he adds. In the meantime he remains confident of the international standing of the UK in biomedicine. The available measures suggest that Britain still contributes more than its fair share, and he's encouraged by the level of Government and charitable sector spending. But at root, he insists, it's about people. 'Medicine and medical research are still attractive to young people in this country, and that's really crucial. We have to hang on to that.'

The President in profile

The 30 years or so that Professor Sir John Bell FRS PMedSci has spent in the UK have done little to diminish his North American accent. Nor have they blunted the unstuffy and direct manner with which he expounds his enthusiasm for the medical science that has shaped his career, and to which he has contributed.

Born in Edmonton, Canada to an Anglophile father, a haematologist, he came to Britain to study medicine as a Rhodes Scholar. Having liked what he found, he stayed for a further period after qualifying, and then moved to Stanford. At that stage he had no plans to return to the UK – the more so given that the timing of his move to Stanford had been exceptionally fortunate. 'I arrived in a lab that was cloning all the HLA genes [of the major histocompatibility complex] for the first time. It was just fantastic. But I wasn't that comfortable living in America, and I couldn't see myself spending the rest of my life in California. So after five years I looked around.' Professor Sir David Weatherall invited him to return to Oxford and join the Institute of Molecular Medicine, initially for five years. But the work went well and once again he stayed on, becoming the Nuffield and then the Regius professor. The environment - UK in general, Oxford in particular - suits him. 'Once in the position of Nuffield professor I was able to think rather more strategically about the big issues in medicine, such as genetics and epidemiology, and how you deal with them,' he recalls. He co-founded Oxford's Wellcome Trust Centre for Human Genetics, and built up a research programme on the genetic determinants of susceptibility to diabetes and rheumatoid arthritis. He chaired the UK Biobank Science Committee, has acted as a scientific advisor to pharmaceutical companies, and has also served on numerous research bodies such as the MRC and UKCRC.

John was one of the founder Fellows elected to the Academy in 1998 and he became President in 2006. He is also the Chairman of the Office for the Strategic Coordination of Health Research (OSCHR). In 2008 he received a knighthood for his services to medical science and was elected a fellow of the Royal Society.

Dr Geoff Watts FMedSci

Geoff Watts graduated in zoology and spent five years in medical research before deciding to abandon the laboratory in favour of the pen and the microphone. He was deputy editor of the magazine 'World Medicine', and presented the BBC Radio 4 programme 'Medicine Now' throughout its 17 year existence. As a freelance journalist he has presented numerous programmes on science and medicine for Radios 3 and 4 and the BBC World Service. He currently presents the Radio 4 science weekly 'Leading Edge', writes, lectures, and sits on too many committees. He spent six years as a member of the Human Genetics Commission, and was elected a Fellow of the Academy of Medical Sciences in 2003.

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