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Professor Sir John Bell, President of the Academy of Medical Sciences

Geoff Watts

As part of the Academy of Medical Sciences' 10th anniversary celebrations, I conducted a series of interviews with its president Professor Sir John Bell. 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

Does Sir John 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 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 healthcare 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. That Bell 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 it the early 70s, but the first therapeutic antibodies appeared in the mid-90s.…You have to take the human genome in that context. Genetics and genetic manipulation really emerged in the mid-70s 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 80s. But the sequencing of the genome and an understanding of the variation within it only came in the early to mid-90s. 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 led 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, 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 is 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% of a population of patients with a particular disorder:

> *If you take a drug which, in a large randomised trial, gives you an efficacy of say only 30% over placebo, but you then identify those 30% 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%, 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 is 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.*

Twenty years ago only a handful of known gene variants had been associated with a predisposition to a common disease. By the beginning of 2009, says Bell, there were 130. By the end of it there will be over 200 and, by the end of next year, 400:

Geoff Watts, Science Broadcaster and Fellow, Academy of Medical Sciences

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!

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.

Bell 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.

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.

The policy decisions that need to be taken involve economics, education, changes to the way we live, and much else:

The World Health Organization is very good at managing infectious disease problems, but has yet to seize on chronic diseases in a serious way. It spends only about two to three percent 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 have not 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 beta cells:

In the 80s and the early 90s, 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?

The investigation of diabetes at the molecular genetics 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, Bell 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 the core, Bell 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 has not 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 will not 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 is 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, Bell 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 sees as a greater willingness within the NHS to consider innovation.

It would be wrong to imply that 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 does not cause the disease. As discussed in the academy's latest report entitled *Brain science, addiction and drugs*,[1] 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.

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, tuberculosis, 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.

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 [the academy] 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 policymakers 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. '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 is 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'.

Reference

1 Academy of Medical Sciences. *Brain science, addiction and drugs.* London: Academy of Medical Sciences, 2008.

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