

interview

Sir David Weatherall reflects on genetics and personalized medicine

Interviewed by **Ulrike Knies-Bamforth**

Tell us a bit about yourself and your career so far

For the last thirty years, I've been in Oxford, first as the Nuffield Professor of Clinical Medicine, then Regius Professor of Medicine. In 1989 I founded the Institute of Molecular Medicine here in Oxford. Since retirement I've been spending a lot of time in the developing countries and did a report on the application of genomics for global health for the World Health Organization and I've been interested in trying to apply some of the technology of molecular genetics for problems of the third world.

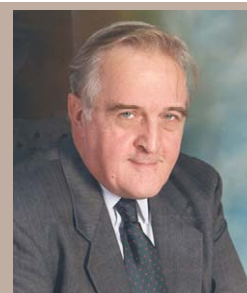
'We concluded that a better understanding of genetics and drug metabolism is likely to improve the efficiency of drug development by the pharmaceutical industry.'

You recently chaired the Royal Society report on personalized medicine. For the benefit of our readers, could you briefly sum up the conclusions of this report?

The report revolves largely around pharmacogenetics because it is one of the major areas in

Sir David Weatherall

David Weatherall qualified at Liverpool University, UK in 1956 and, after a period of National Service in Malaya, spent four years at John Hopkins Hospital, Baltimore, USA. He returned to Liverpool in 1965, where he was appointed Professor of Haematology in 1971. In 1974 he moved to Oxford, UK, where he was Nuffield Professor of Clinical Medicine until 1992. In 1992 he was appointed Regius Professor of Medicine at Oxford. In 1979 he became Honorary Director of the MRC Molecular Haematology Unit, and in 1989 he established the Institute of Molecular Medicine at Oxford (later named Weatherall Institute of Molecular Medicine), of which he was Honorary Director. His major research contributions, resulting in some 700 publications, have been in the elucidation of the clinical and molecular basis for the thalassaemias and the application of this information for the control and prevention of these diseases in developing countries. He was knighted in 1987, elected FRS in 1977 and became a Foreign Associate of the National Academy of Sciences, USA, in 1990. In 1992 he was President of the British Association for the Advancement of Science. He became Emeritus Regius Professor of Medicine in September 2000 upon his retirement, and was appointed Chancellor of Keele University in 2002.



which people who have talked about personalized medicine have centred their argument. We concluded that a better understanding of genetics and drug metabolism is likely to improve the efficiency of drug development by the pharmaceutical industry. We were a lot more cautious about the immediate application of personalized medicine in the clinic. We felt that one of the major possibilities in the medium-term would be that the genetic analysis of common diseases could well show that what we now think is a single disease has multiple different causes, which would undoubtedly produce more focused and targeted medicines. We already have a very good example in the cancer field, where what we used to think of as one type of cancer, for example lung or breast cancer, now turns out to be a group of several different

diseases and it has already been possible to target treatment more logically.

We were more cautious as to how the knowledge of an individual's genetic make-up would be applied broadly in clinical practice. There is this idea that in 20 years time a general practitioner would have a printout of your genome on the desk, and if you came in with a headache he'd press a button and tell you if you're a one- or two-aspirin person. This could be a long way off – if ever! Take, for example, a commonly used drug like warfarin, which we've known (for 40 years) has genetic variation in its metabolism, and we now know that there are at least two genes involved. But nobody has yet done a large community study to ask whether it is cost effective and clinically effective for the patient to know their genetic make-up before

they start the drug. In other words, is the genetic approach to treatment better than what is being done at this time, which is simply the monitoring of dose against effect and careful monitoring for side-effects?

So we were much more cautious about the practical use of pharmacogenetics in the community. And then, finally, we discussed the organizational and ethical issues: who is going to hold this genetic information, who is going to do the genetic testing, who is going to advise the patient? Is it the hospital, primary care doctor, nurse or pharmacist?

'A lot of progress has been made in defining the genetic variability to drugs, and many drugs are probably metabolized by more than one gene.'

Could you briefly explain why, although a lot of progress has been made in personalized medicine, particularly in the field of cancer, you still think that real progress is 20 to 30 years away?

We're just starting to see targeted therapy for this common disease. It's still too early to say how effective it's going to be, and to what extent new mutations in cancer cells will lead to resistance to targeted drugs. So I think the full picture is not yet clear. Other disorders, such as heart disease and diabetes for example, are probably heterogeneous as well. There's a large environmental component and there are probably many different genes that can make you more or less susceptible. A lot of progress has been made in defining the genetic variability to drugs, and many drugs are probably metabolized by more than one gene. So, as I explained for warfarin, moving from the research laboratory to something that is going to be of day-to-day clinical value is a long time ahead. Because of all the hype since the genome project was successfully completed, particularly about its clinical value, we needed to get a hold on the issue and say 'look, be careful in planning healthcare, some of this is going to take a long time to be worked out'.

So other than the field of cancer, which other field do you think is going to benefit from personalized medicine in the near future?

This is very difficult to say. I suspect that type 2 diabetes, which is insulin-resistance diabetes associated with obesity, for which we are now seeing a world epidemic, might be a different disease in different populations and have different causes. There have already been a couple

of examples of rarer forms in childhood, where defining the precise cause has made rational therapy possible. It's highly possible that certain diseases of the nervous system are also suitable for personalized medicine. Because, according to WHO, we're all going to be depressed, and by the year 2020 bipolar depressive illness is going to be the major cause of ill health, we'd want to be able to treat it more logically. There has been some progress looking at the genetics of drugs that are used to treat depression and, I believe, large community trials similar to those for warfarin have started, so I can see gradual snipping away at progress in those two common diseases.

Is there anything that can be done to accelerate the process of bringing personalized medicine into the clinic?

To my mind, perhaps a slight change in attitude in the research community and, as usual, more funding. Although there is some beautiful work going on in this field, the really difficult stage is when you take your basic information that a drug does have a strong genetic component in its metabolism and move on to do the boring but vital studies in the community, as I was explaining for warfarin.

You've got to take a large number of people in the community and either treat them knowing their genetic make-up ahead of time or in the present way, that is careful monitoring. The aim is to find out whether knowing the genetic component is cost effective and also patient effective. And that's got to be done drug by drug; there are no short cuts.

In the long-term, do you think that personalized medicine will change the face of medicine and that prophylactic medicines will become more popular? Can we actually afford to treat everyone prophylactically and how likely is it that this is going to be successful?

Well we're doing it at the moment, aren't we? Most old people are wandering around with massive arsenals of drugs. We are following the notion of prophylactic treatment of cholesterol until your cholesterol is at the level of a Chinese field worker; your blood pressure has to be controlled by another set of drugs, and so on. If you're personalizing all that, instead of taking the blunderbuss approach, which is the standard dosage for everybody, you would be genetically testing the patients and perhaps in a few cases you might find that it's cost effective to do that. However you do it, I can't imagine it's not going to add another enor-

mous level of cost to healthcare. If you could keep a large number of people out of hospital because you avoid side-effects of drugs it would probably be cost effective, but until you've tested a few drugs in this way we just don't know. If you ask me that question in five or ten years time when we know that it is effective for management, as well as in terms of cost, to do simple genetic tests for one or two commonly used drugs then you can answer that question. At the moment, we don't have any idea. Curiously, some epidemiologists are advocating that all of us take a 'wonder pill' to control our blood pressure, cholesterol and more – from middle-age onwards. Even this de-personalized medicine will be very costly. Will we then have to have several different wonder pills based on our genetic make-up?

'...the day of the blockbuster might be over and [pharmaceutical companies] will have to reorientate their way of thinking.'

Would pharmacogenomics, if it was feasible, not just cut up the market and make this concept completely unattractive to big pharma – who don't seem to have financial models for drugs other than the blockbusters?

Yes, there is that danger and the pharmaceutical industry is well aware of it. In the cancer field you now find that a drug is, perhaps, only effective in a small percentage of patients. This will have to be watched very carefully. Governments and health agencies will have to come to grips with the possibility that they might have to come to financial arrangements with companies. In fact the representatives of pharmaceutical companies that we talked to admitted that, probably, the day of the blockbuster might be over and they will have to reorientate their way of thinking.

So do you think that when it comes to developing personalized medicine smaller biotech companies are more likely to take the lead than big pharma?

Yes, I think that's probably right, at least as judged from our enquiries; I'm not close to industry. However, big pharma's R&D policies are changing. They are moving away from looking for the heterogeneity of disease to using genomics in drug development to avoid side-effects. I think academia and smaller start-up companies might have to be much more involved in what you might call the clinical

applications of pharmacogenetics; big pharma will not do this for us.

'...it is now possible to define drug resistance at a genetic level in organisms...'

Do you think that there is a role for personalized medicine in the third world setting and is it practical and economically feasible yet?

Well, again, the cost-benefit studies have not been done. Taking a fairly broad definition of pharmacogenetics, there are situations in which it would be enormously helpful. For example, it is now possible to define drug resistance at a genetic level in organisms, like the malarial parasite. So you can anticipate resistance much earlier. But is this clinically and cost effective? There is undoubtedly human genetic polymorphism for response to some of the antimalarial drugs and drugs used in HIV. No one has actually done a field study in Africa, for example, to ask whether this information would be of clinical value, particularly if the genetic test was simple? When you are treating huge numbers of people, and at the moment they're not even getting treated because their health delivery programs are not good enough, how on earth can you think about genetic testing? However, if the genetic variation has a major effect on efficacy or toxicity there could be a role. For example, there is a form of malaria caused by an organism called *Plasmodium vivax*, which is very common, particularly in children all over Asia and the Indian Subcontinent, although less so in Africa. There is only one drug that is effective and now we are beginning to see early resistance to that drug. The situation is that in India, for example, we need to extend the period of treatment by ~50%. There is a common genetic polymorphism (glucose-6-phosphate dehydrogenase deficiency), which affects between 5–10% or even more of those populations, and which makes patients sensitive to that drug so that they develop severe anaemia. It is important, particularly for patients on longer courses of treatment, that we should test for this polymorphism. The test is a very simple chemical test but at the moment but it's still too complicated. What's most urgently needed is a simple dip stick test for enzyme deficiency. That's the kind of thing that really would make a difference, provided that it was not expensive. Where I work now, in parts of India and Sri Lanka, unless a screening test costs a few Rupees, forget it. They can't afford the drugs, never mind the screening test. So I think it might be possible if

we were to reduce the price of the particular genetic tests.

So do you think that the World Health Organization should be supporting efforts in developing such a simplified test and, therefore, speeding up the application?

Yes, and they do know that. That's certainly been on the agenda of their genetics committees for a long time now.

Do you think that there is a difference in the progress of developing personalized medicine when you compare the UK to the USA?

In terms of sheer volume, there is a lot more pharmacogenetics work going on in the United States. A problem, which we consider in the report, is that pharmacology as a speciality in the UK has taken a real knock over the past ten to twenty years. For a variety of reasons, it has not been taught as well as it was and there are fewer clinical pharmacology departments. So the work is being done within individual specialities, like cardiology. Because of the rather poor training in pharmacology in medical schools, a lot of people do not have the basic understanding of drug metabolism. For that reason, and for perceived lack of support, one of our most successful pharmacogenetics groups working in the neurosciences has recently moved to the USA. Yes, there is a lot more basic science in the USA but the important follow-up community studies are not so active. In some ways the health care system in the UK is ideal for doing those. It is much more difficult to do the same studies in America. So yes, we are lagging behind a bit on the underlying science, but I hope we can catch up on and do better than them in the more practical applications.

'The most exciting prospect will be to bring basic research in genetics into partnership with epidemiology and medicine in the community.'

Do you think we have too much faith in modern technologies such as molecular medicine? If you had one million pounds do you think it would be better spent understanding an apoptotic pathway in cancer or investing in a hospital for the terminally ill? As the population ages, there might be an increasing demand to move away from the whole technology-based look at research and technology?

That's an enormous question to answer in a couple of sentences. Well, let me take it first of all from a scientific point of view. This (the Weatherall Institute of Molecular Medicine) is the first institute in the country that brought clinicians and molecular biologists together, so I'm slightly biased. But I think we've become perhaps over-directed towards genomics and molecular biology approaches to medicine over recent years. And probably have raised too many expectations because it's a new field and it's been so exciting from the biological point of view. Despite advances in systems biology we will have to move back to what you might call whole animal or whole human type of research before we really understand how the human genome works. What doesn't seem to have been appreciated is the enormous complexity of human disease: layer upon layer, and strong environmental and social components. We have to get our medical students to understand this better because at the end of the day the art of medicine is not going away. Everything is so unpredictable and will remain so, however much you know about genetic susceptibility and disease mechanisms. A lot of medical care depends on experience, and also, decent human kindness. This will not change. I think it would be disastrous if we stopped funding basic research. But what we've got to do is make sure that there is a balance between that and research in individual patients in large communities. The most exciting prospect will be to bring basic research in genetics into partnership with epidemiology and medicine in the community. That's why in Oxford we built the new Richard Doll building (for epidemiological research) next door to the Wellcome Trust Centre for Human Genetics. If I had a million pounds I would give it to a research group that combined genomics with classical epidemiology and, in particular, the detailed study of disease phenotypes, and then set it loose on a pilot study involving a common multigenic disease.

Another area I wanted to hear your thoughts on is the patent system. Can you say that the patent system is stifling progress, particularly for the third-world countries? And on a related note: is the fear of litigation putting developing drugs at risk?

We didn't deal with this issue much in this recent report. I tried to deal with it when I was lead writer for the report *Genomics and World Health* for the WHO a couple of years ago and we got

into a lot of trouble because certain countries didn't like our criticism. There are two main issues here. First, there is the question of patenting DNA and proteins. There is still fighting over this issue. Can you bang a patent on a DNA sequence or proteins? When is it acceptable to patent a protein? A DNA sequence and a protein are natural products, there to be isolated. I know there has been some progress by having to prove a novel inventive use for them. But there have been so many of these patents already that this is bound to produce problems in the future. They are soluble; it simply requires some real common sense being drummed into the whole patenting process. The second issue is how to supply the developing world with the drugs and vaccines that it needs. Of the 1233 new drugs marketed between 1975 and 1999, only 13 were approved for tropical diseases. How can this balance be redressed?

Another unrelated question, you've been involved in the work on thalassaemia. It was known that in this disease there was a connection to the globins. Do you think it would have been possible to find this connection with modern genetics studies like linkage-association or using single nucleotide polymorphisms?

This is an interesting question. I think in a monogenic disease with a very strong penetrance you probably would. Our colleagues from Thailand have recently been doing a major genome hunt for modifiers of thalassaemia and one of the modifiers they found, which we've known about for some years from family studies, is in the β globin gene cluster. I would have thought that with a highly penetrant disease like that, with any luck we might have got it. We found the position of the gene for polycystic kidney disease by simple family

linkage studies using polymorphic regions near the α globin gene. I think the answer is yes, if one had one or two good polymorphic regions and if one was lucky one probably would have done.

To finish the interview off, what career achievement are you most proud of?

I suppose getting in early and applying techniques for protein chemistry and then molecular biology to study the most common genetic diseases like thalassaemias, and seeing that at least some of that information surprisingly quickly could be applied for controlling these diseases in the community. And I am pleased to have set up a place like this (the Weatherall Institute of Molecular Medicine) to bring clinical and basic scientist together under one roof and to find that they still speak to each other after 15 years!

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