Translating metabolic biochemistry into the clinic: an interview with Steve O'Rahilly

Professor Steve O'Rahilly is one of the UK's most renowned clinical researchers. He made his reputation by combining clinical practice with scientific and clinical studies focused on understanding the causes and consequences of obesity and insulin resistance. Here, he talks about his research philosophy, and his wider role as a spokesman for obesity research.

Professor Steve O'Rahilly was born in Dublin in 1958. After attending medical school in Dublin, he left Ireland for postgraduate research in London, Oxford and Harvard, and in 1991 moved to Cambridge to run his own laboratory at Addenbrooke's Hospital, where in 1996 he was appointed to the Chair of Metabolic Medicine. In 2002 he was appointed to the Chair of Clinical Biochemistry and Medicine at the University of Cambridge. He is currently Co-Director of the Institute of Metabolic Science (IMS) and Director of the IMS Metabolic Research Laboratories. His research programmes involve identifying biological causes of these problems in patients, supported by studies in cells and, where necessary, animal models. He is especially keen to apply lessons learned from such experimental studies to advance the diagnosis and treatment of patients with metabolic and endocrine disorders. While maintaining a large research laboratory he continues to be actively involved in clinical practice and the teaching of clinical medical students.

You've been at Cambridge for most of your career, hired in the 1980s straight out of your postdoc at Harvard. Why Cambridge? I know it was considered a bit of a clinical backwater in those days.

Well, several senior medical colleagues at the time expressed some surprise I was going to Cambridge. It was only in the 1970s that Cambridge first started teaching medical students through to qualification and, until pretty recently, most of its medical undergraduates went on to London to complete their training. Although there had been some important clinical research emanating from Cambridge (notably Roy Calne's work in organ transplantation), it was only with Keith Peter's arrival as Regius Professor of Physic that Cambridge really began to exploit the co-location of a world-class university with a growing teaching hospital serving a burgeoning local populace. Despite the doubts of some of my advisors, I felt Cambridge was ripe at the time – it was a very exciting place to arrive in. Keith is a hugely driven and dynamic person. It was a great scientific environment but they had few clinician scientists, so they were very keen to have me as I was someone who could link the lab to the clinic. Nick Hales was head of Clinical Biochemistry then, and he'd identified a lot of patients who had spectacularly elevated serum insulin with no obvious reason. Ken Siddle, an insulin signalling expert, could help us work out the basic signalling faults if we found any genetic defects, and we also had John Hutton, who was a superb researcher in insulin secretion. For the first couple of years my own lab didn't discover anything very revolutionary, but we were developing the ability to go from patient to gene to cellular function and then back again – we were starting to make some mechanistic sense of patients' problems, and that was new and exciting, at least to me!

So, you're clearly no longer a backwater!

Over the last 20 years, many clinician scientists with a similar background to myself have grown up together on this campus. It's been fun to populate this place; if you had looked out of the window here over the last couple of decades you would have seen the transformation from a small district hospital [rather oddly co-located with the research behemoth of the Medical Research Council (MRC) Laboratory of Molecular Biology] to a situation where the Clinical School and hospital are now core parts of a really buzzy, dynamic medical/academic/scientific campus.

What has the Cambridge science establishment made of you all then?

It's been interesting. Of course, Keith was crucial in trying to convince the university scientists that "hey, there may be something worth thinking about in clinical translational

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science". He really broke down, or at least attempted to break down, a lot of those barriers. I think the relationships now are really good – everyone is on the same page. There's much less of a barrier between what's seen as basic science and what's seen as translational clinical science. We have institutes like the Cambridge Institute of Medical Research, which has 50% clinician scientists and 50% basic scientists. My own lab has multiple collaborations with people both downtown in the basic science departments and in adjacent MRC units up here at the Addenbrooke's Hospital site. We are becoming much more of a unified and complementary place.

You've said before that the most effective way to do your kind of disease-oriented research is for one person to be both basic researcher and clinician. Do you still think that's the case?

If you're going to try to exploit the natural human variability exhibited by patients who present their symptoms to doctors to try to better understand human biology, then there is a huge advantage in being someone who can operate in both spheres. This is a very exciting time in human genetics. If we study an extreme human phenotype, we now have a very good chance of finding its cause even if we've got no obvious family material available. As an example, within the last week we've established the molecular basis for two new human metabolic disorders that result from de novo mutations. Previously, we would never have embarked on genetic studies in these cases because there were no affected family members to establish co-segregation. Now, with whole-exome sequencing, there is a real opportunity to maximally exploit human genetic variability to better understand human biology and to discover previously unknown diseases. In some cases these discoveries immediately suggest new mechanism-based therapies, which is enormously exciting.

Do you see human genetics and animal models working in tandem?

Absolutely. At the moment, some of the work we are doing that excites me most is being undertaken in model organisms, but I still think that we have learnt a lot from studying humans. For example, leptin was discovered after more than 50 years of basic science culminating in Jeff Friedman's discovery in *ob/ob* mice. However, there are examples, such as in prohormone conversion, where human genetic discovery has preceded the murine work.

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It's clear that we're moving away from the old linear pathway of 'clever discovery' in mice followed by 'boring studies' in man to prove human relevance. The relationship is going to be much more bidirectional. Things are already changing profoundly due to the proliferation of GWAS (genome-wide association studies) data – even if some people are being sniffy about GWAS and what they've told us. I think that when the dust settles on this area you'll find that GWAS have informed us about quite a lot of new biology. For example, the most common obesity variant is in a gene called *FTO*. Now, *FTO* turns out, bizarrely, to be a member of the AlkB DNA/RNA demethylase family. None of that has come from animal work; it's come from a human genetic observation, and now we're learning about an entirely new biochemical pathway which has of course required murine manipulation to prove that it's *FTO* that's the causative gene. We're going back from human genetics through mice and now into the cell biology. I think what you will always be able to do with murine models that you won't be able to do with humans is to undertake elegant tests of physiology, because you can tissue-specifically and temporally alter gene expression and protein function in a way you never can in a human being. So, you will be able to understand the impact of a genetic variant on a particular tissue or a particular system only by studying it in the context of a genetically modified organism. I don't see an 'us-versus-them' scenario at all.

Do you think there's still a lack of connection between basic and clinical researchers?

Clearly, if you look at the focus of basic science, it's on molecules whose role in important human diseases has been validated through human genetics. However, there is often a longish lag time between a human genetic discovery and it filtering into the interests of the strongest basic scientists. So, yes, there is sometimes a bit of a disconnect between these two fields. I think one of our jobs is to try to reduce that disconnect between human genetics and the functional evaluation of the basic properties of key molecules with a real role in human disease.

You're renowned for your discoveries of previously unknown genetic metabolic diseases. What gave you an edge over your competitors, and do you think there are many more disease subtypes still out there?

We've had a lot of fun over the last 15 years, because we've made educated guesses – some of which have been right. I think the main reason we got it right is because we chose really extreme phenotypes. People that are not clinicians don't tend to see the difference between the ends of a population distribution in an epidemiological survey and an 'ultra-extreme' phenotype. But if you've got something that strikes an experienced clinician as being really out of the ordinary, there's got to be some fundamental disturbance of homeostasis, which is more likely to be a highly penetrant allele. That's really what we've based our discoveries on – we've not been too bothered about how common or rare these things are. They'll teach us about human biology even if there's only an *n* of 1 in the world.

I'm feeling very bullish at the moment, because there's a child I went to see in Great Ormond Street some 12 years ago and we've been struggling all these years to understand what's going on with their particular condition. I don't want to steal my colleagues' thunder, and it's early days yet, but as of last week we've got the answer, and it's beautiful. It's a generalisable story and it's one we think we may be able to get a therapy for. So that's the excitement – you can find things that are elegant, but also that you can do something about.

When you tell people who are obese and ill that it's not their fault – that there's a biological basis to it – how do they react?

People respond in very different ways. Clearly, if you have a genetic defect that we can do something about, like leptin deficiency, we can actually restore

homeostasis and normal weight, and then it's transformative, but that's very rare. You get a range of responses among patients who have been obese for a long time and have suffered both the medical effects and the social vilification of being obese. Some of them feel hugely relieved of the guilt that they have been made to feel; the medicalisation of it validates their having known all along that they're different. Others are rather depressed by it; they feel they have an intractable underlying problem which is not likely to be readily overcome. I try to put a positive spin on it: if we can find enough people with a set of specific defects then we can much better target our trials. My approach to genetics is that it's a bit like establishing what the wiring diagram is under the car bonnet. It's only the first step to a better understanding of how we might bypass the genetic defects and find therapeutics. That's one of the aims of our current and ongoing research.

What is the interest of drug companies in treating very small subsets of massive problems?

Drug companies really are open to this, given the difficulties of drug development over the last 10-15 years. It's been realised that perhaps one of the barriers in drug development has been a failure to recognise that so-called common diseases are made up of multiple different types of disease. So, stratified medicine is a huge area of interest for the pharmaceutical industry at the moment. They're very interested in what we do for the same reason that we are interested; our work helps to identify control pathways and say that this or that molecule is critical for a function like energy balance or insulin action. This sort of deep background information is very important for the pharmaceutical industry. Quite a bit of our work is done in collaboration with industry, as we're very keen to see our work lead to therapeutics. In the case of leptin, for example, we first described the biological action of leptin in children who are genetically deficient for it; this is a very rare condition – maybe identified in 20-25 children worldwide. Leptin as a therapy was then tried in patients who lacked leptin because they lacked adipose tissue due to lipodystrophy – that's a much more common condition. Now there's going to be an orphan drug indication for lypodystrophy, and there will be more chance to look at subtypes of regular obesity, and even subtypes of reproductive dysfunction. My guess is that once investigators do targeted trials, we'll find that there is a gradual increase in the remit of drugs that started out as treatments for rare entities.

I was intrigued to hear you say a couple of years ago that there might be a degenerative brain disease similar to Alzheimer's that was affecting appetite control.

That was a wild speculation and remains so! The idea is as follows: we find all of these very obese kids, and the trajectory of their obesity is that they become obese very quickly then they stay parallel to normal centiles – it's as if homeostasis has been tweaked and is wrong, but it's wrong at a regulated level. Then there are the people you hear about where a ball and chain has to be taken to the side of a house to take them out as they're so massively obese they can't get into a hospital bed. When you get a chance to see them, you don't get the same history as with obese children: you often get a history of someone who was of normal weight in childhood and gradually but relentlessly increased in weight year on year. The explanation that most people have is that these are sad people who stuff themselves to death because they are unhappy and the fatter they are the unhappier they get. Intuitively, that just doesn't seem right to me. There seems to be some fundamental flaw in that, and the sort of trajectory suggests to me a degenerative disorder – that things are getting worse every year. And of course neurons are at the heart of the central appetitive control, so if you had a progressive dysfunction of those neurons you might end up with a central nervous system that's incapable of controlling appetite and energy balance. If you look in the literature, there's not been a systematic attempt to do even the basic histomorphometry of brains of people with that sort of progressive obesity at post mortem. It's something I have in the back of my mind to write a grant for. I think that any sort of study of this will need a systematic approach across the whole of the UK – it will need to use brain banks.

I'd also like to ask you about the public face of your research.

My approach is to try to get across to the public that despite the fact that there are undoubtedly environmental drivers for the recent increases in the prevalence of obesity, the susceptibilities of individuals to these drivers are hugely different, and have a very strong genetic basis to them. That concept should lead to a somewhat more sympathetic attitude towards people with obesity. There are few human conditions that result in such vilification and such lack of acceptance as does obesity. For some reason, it seems to hit a chord – it's the last remaining 'ism'. We can't be sexist, we can't be racist, but you read the popular press and there are things said about people who happen to carry excess adipose tissue that are just unspeakable – much worse, for example, than people who park in disabled parking spaces when they are able bodied or people who cheat on their spouses. Obesity doesn't particularly impact anyone else other than the sufferer and yet it results in this dreadful vilification, which I find very hard to understand. I hope what we do can at least change some people's minds. It's been very gratifying at talks to have people come down and say, "You know, that is so compelling – and I never knew about it". Anyone with an ounce of scientific nous couldn't go away from a talk I give about the genetics of obesity and say I don't believe that genes have anything to do with being obese – it would just be ridiculous having seen what the data look like. I am emphatically not saying that approaches towards reducing portion size and improving the quality and quantity of food we eat aren't important – of course those things are crucial – but I want people to see that there is another side to this issue.

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Do you think it's somehow politically expedient to downplay what you're saying – that is, that people won't pay as much attention to their health problem if they think it's not their fault?

There is a fear that if people think their condition is predetermined then they won't try and do anything about it. I think some of my colleagues who work in public health environments are concerned that what genetics finds will have an adverse effect on people's willingness to try and change. What I can say is that I think it's always better to

know what the truth is and then deal with it, rather than hide the truth. I think that's been a basic premise of science for as long as I can recall.

You've previously used the very apt analogy with the medication of high blood pressure.

The beauty of treating high blood pressure is that, as well as taking dietary measures, we now have four different classes of drugs which cost pennies; they're generic and cheap, they're pretty effective and they're not that complicated by side effects. There are very few people in the UK with blood pressure that can't be controlled and we think nothing of it; you don't go around saying, "Ooh look at you, you high-blood-pressured person – why don't you just eat less salt and not take those morally repugnant tablets?". Weight has a similar variability to blood pressure and a similar association with adverse health outcomes, yet societal attitudes to obesity and hypertension are very different.

Do you think such drugs would be possible for obesity?

I think it's a tougher field to work in but I think that they really should be possible. It will probably be based on combination therapy. It might start with the natural products of our intestinal endocrine cells that have an effect on appetite suppression. It might even involve a combination with leptin; even though leptin has long been thought to be dead in the water as a treatment for obesity, as a combination with gut-derived peptides it has definite promise. In the case of leptin deficiency, we've seen children who were wheelchair bound with obesity who, within 6 months of therapy, are now normal. Seeing that on a relatively regular basis gives one tremendous optimism: if there's one scenario in which that can be done it would be ridiculous to conclude that it can't be done in other cases – we just need to be cleverer.

So you remain an optimist?

Yes. But perhaps a 'possibilist' would put it more accurately!

Excerpts from this interview can be heard in the podcast associated with DMM Vol. 4, Issue 2 at http://www.biologists.com/DMM/podcasts/index.html. DMM greatly appreciates Steve O'Rahilly's willingness to share his unique thoughts and experiences. Steve O'Rahilly was interviewed by Kathy Weston, Consulting Editor for DMM. This piece has been edited and condensed with approval from the interviewee.