

A conversation with Stephen O’Rahilly

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Conversations with Giants in Medicine

Professor Stephen O’Rahilly’s research has led to an increased understanding of the genetic causes of human obesity and insulin resistance. Using modern biochemical approaches and classical clinical observation in humans with profound metabolic disorders, O’Rahilly (Figure 1), from the Departments of Medicine and Clinical Biochemistry at the University of Cambridge, has shown that a person’s appetite and feeding behavior can be linked to specific genes. His work has challenged long-held dogmas and led to new treatment avenues. The full interview, with many more stories about how you can learn more from reading Chekhov than medical school and why he has stayed in Cambridge all these years, can be seen on the JCI website at <http://www.jci.org/kiosk/cgm>. JCI: Where did you grow up and what was your path to medical school like? O’Rahilly: Ireland, unlike most of Western Europe, didn’t benefit from the postwar boom. It was a pretty gray place for the first 20 or 30 years after the war, and my generation was really the first to go to university. My father was, for many years, an apprentice in a pharmacy. And when he met my mother, she injected some ambition into him and made him do night classes. He became a trained pharmacist, and then he set up shop in a blue-collar suburb in the north of Dublin. I [...]

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JCI: Where did you grow up and what was your path to medical school like?

O'Rahilly: Ireland, unlike most of Western Europe, didn't benefit from the postwar boom. It was a pretty gray place for the first 20 or 30 years after the war, and my generation was really the first to go to university. My father was, for many years, an apprentice in a pharmacy. And when he met my mother, she injected some ambition into him and made him do night classes. He became a trained pharmacist, and then he set up shop in a blue-collar suburb in the north of Dublin.

I read from a very early age and, even in the little school I went to, there was some fluster about the fact that I could read so early, and they sent some inspectors in and tried to work out was there something odd about this kid. I read avidly and I read widely, and some of the things I read were science-related. One of my memories of childhood was asking my dad to buy me *Scientific American* and being really thrilled by some of the biology. A book that had a huge influence on me was Lewis Thomas' *The Lives of a Cell*. I think I read that when I was 14 or 15, and I was absolutely fascinated that you could see these macroscopic problems and then actually they could be drilled down to the molecular and atomic level. I thought medicine, as a career, could provide a perfect combination of science with something that would be useful to people.

JCI: What stoked your interest in research?

O'Rahilly: Dublin was a wonderful place to train as a clinician, but there were very few role models as researchers, so I went

to England. At Barts, and then the Hammersmith, I got great residency training and really loved clinical medicine. I then thought, at that stage mainly for career reasons, I had better do some research. I met this wonderful man, Robert Turner from Oxford who offered me a year of soft money – at the time I had no research background and I wouldn't have been able to get funds to do a PhD. I loved it. I then decided that clinical academia was the career for me.

JCI: The research with Turner was on genetics?

O'Rahilly: It wasn't initially; it was on the physiology. We looked at people who were first-degree relatives of patients with type 2 diabetes and asked if we could discern if they had pancreatic β cell abnormalities at an early stage. But then the world changed through the revolution in molecular genetics being applied to medicine. At the epicenter of that was David Weatherall's unit in Oxford where, for example, the first DNA based genetic linkages to autosomal disease such as polycystic kidney disease were being found. The excitement of this was palpable in Oxford at the time. And so I thought that if I was to be serious about being a clinical academic, I had to get into this stuff. Robert was generous and prescient enough to allow me to spend a year learning molecular biology. I ended up doing some of the first linkage studies in type 2 diabetes. The studies were very naïve. Looking back now, they were grossly underpowered and entirely based on restriction fragment length polymorphisms detected by Southern blotting.

JCI: Then from there, you landed at Harvard for a little while before establishing your lab at Cambridge.

O'Rahilly: That time had a huge impact on me. In terms of results, I discovered almost nothing in the two years that I was at Harvard. But I discovered approaches and ways of thinking, and I also discovered what I couldn't do. I went to the Mass General to Joel Habener's lab to clone the GLP1 receptor, which turned out 20 years later to be the biggest therapeutic target in type 2 diabetes. So I was absolutely right to want to do that at that stage, but I discovered when I got there that I couldn't do it. After six months of blood, sweat, and tears trying to do cesium columns for RNA preps and failing, and breaking things, I figured I'd better get back to my roots in the interface

between clinical observation and the application of new technologies.

I went and joined Jeff Flier in a much more clinically oriented lab, examining patients with severe insulin resistance. I knew that in Cambridge, my predecessor Nick Hales had a set of patients with very high insulin levels that they didn't understand the basis of, and I thought that I could come back bringing the tools I had learned in Harvard, set up my own little lab – I had only one technician when I started in '91 – and start working on this group of patients to try and see if I could understand why they were so insulin resistant.

JCI: While the bulk of your studies have been in the human, there was one instance where the mouse informed your work, the *ob/ob* mouse with its defect in leptin. How did you come across the first humans – the Punjabi cousins who were the first humans found with a defect in leptin?

O'Rahilly: We had been studying children with severe insulin resistance and getting quite a lot of publicity among pediatricians and geneticists in the UK. Obesity is a cause of insulin resistance and I'd been alerted to a patient who had severe obesity and very high proinsulin levels and we found the gene – PCSK1, a very rare defect as only five or six people with this have been found – but that really brought us into thinking about obesity as a biological phenomenon. Around that time, we got contacted by a clinical geneticist who wanted to refer two first cousins who were extremely obese and came from a consanguineous family. This was a few weeks before the Friedman paper had appeared in *Nature*; the human gene sequence had not been cloned at that stage, but we managed to get skin biopsies from these children and got the cDNA sequenced. The amazing story is that we actually missed the mutation. This was about a year before we reported it because it was in a row of six G's that were very densely packed together and the homozygous loss of one G was barely visible.

Sadaf Farooqi, now my renowned professorial colleague and great friend, had joined the lab as a fellow after the *Nature* paper was published and I suggested she use the new leptin assays to revisit and measure leptin in the kids. She came back and said, "It can't have worked. There can't be NO leptin in them." We looked at the old sequencing gels and there it was, having sat there for a



Figure 1
Ushma Neill interviews Steve O'Rahilly in New York City on April 18, 2013. Image credit: Semyon Maltsev.

year. It became apparent we found a potentially treatable form of obesity. Sadaf and I contacted Amgen and started the trial, and the results were dramatic. Within a matter of days these children's food intake were totally normalized. No child had ever been given leptin before, so we had to do it very gingerly, but it became clear it was very safe and now there's about 20 or so kids, and they have all responded wonderfully well. We've been treating one of the patients for 12 or 13 years now. It's a miracle cure, but sadly only for a small number of patients. It is now also working in lipodystrophy, in patients who have severe metabolic defects because they lack fat tissue and therefore have lower leptin. In those patients, it has a great beneficial effect on their metabolic dysfunction.

JCI: Have you ever counted how many mutations your lab has discovered?

O'Rahilly: It comes somewhere between 17 and 20. We've found thousands of mutations in particular genes but I think there were 17 conditions that had not previously been genetically characterized in the realms of obesity, insulin resistance, lipodystrophy, and reproductive disorders.

JCI: How is it that you're so good at finding these needles in the haystack?

O'Rahilly: A lot of a doctor's job is to find out do you fit into an already previously described category and, if the answer is you don't, they throw their hands up in the air. But there are many good physicians and scientists now who are able diagnosticians and can look at patients and their phenotype but have enough knowledge of biology to make some educated guesses. I had a lot of

fun over the years making the guesses. We're also in a totally new era now when you don't actually need to be that smart because, for less than \$1000, you can do a whole exome sequence and give it to a good bioinformatician. Of course, a lot of thought needs to be put into the bioinformatic analysis and the subsequent linking of that to the phenotype.

I went through a very pleasant decade or more where, based on understanding the biology, I could make some guesses about what might be going on and sometimes the guesses were right. But now it is a little bit of "throw it into the mincer, see what comes out the other end."

JCI: How do your patients react when you tell them that there's a genetic reason for their weight gain?

O'Rahilly: Some are delighted that their feeling that they were intrinsically different has been validated. Some even have t-shirts made saying, "We're the MC4 family from..." So they take it very positively, and they're able to tell people why the family looks like that. Others find it rather depressing information, they feel that they have a mark and that nothing can be done to change their situation and therefore, they're irrevocably doomed. That is a whole area of psychological investigation that we really should explore in much greater depth.

JCI: One of the main messages you give in the media is that there's a genetic underpinning to obesity. Why is it that obese individuals are portrayed in the media as being so repugnant?

O'Rahilly: Heritability of obesity is extremely high; apart from height, it's one of

the most heritable phenotypes that we have. I'd hoped we might have changed and shifted things but I don't think we have. I think that the vast bulk of public literature on obesity is condemnatory and is accusatory, and portray the obese as almost uniquely unclean. There's almost no human condition that carries with it so little sense of sympathy.

Naturally lean people like to think they are lean because they are in control and think the obese lack such control. It's very easy for it to be confused with moral choice. I'd like to do a sabbatical in a philosophy department to try and deal with the nature of the repugnance which obesity is viewed. I view it much more repugnant to cheat on your taxes or to cheat on your spouse. Why are those things more acceptable than being fat? Why should it cause such a tremendous reaction?

JCI: I think you need a publicist. Someone who will help deliver the message more broadly as it is pervasive that people assume that the shift in portion sizes and more processed food and more sedentary lifestyles are the sole causes for the increase in obesity.

O'Rahilly: You said two very important things there. You said "sole" and "cause of the increase." These are two concepts that people seem to find great difficulty holding in their brains at the same time. Genetics has nothing to do with the recent increase in the prevalence of obesity. The increase is entirely environmentally driven and nothing I say about the heritability says that we shouldn't be doing something about portion size, about advertising, about encouraging more physical activity. I'm not on the fundamentalist wing of the reductionist biology argument. What I am saying though is that some people are much more susceptible than others; all of the very susceptible are already obese, and we're driving the moderately susceptible into being obese.

JCI: Beyond clinical genetics, and perhaps philosophy as you mentioned earlier, do you have any other vocations that you would have liked to pursue?

O'Rahilly: My perfect life would have been playing on the left wing for Manchester United between the ages of 18 and 35. Then I would be a singer/songwriter a la Tom Waits, or even the best of the Sinatra era, between about 35 and 50. Then I would have won my Nobel Prize in Medicine between 50 and 70, and then I'd finish by writing the great Irish novel. If you could fit everything into a possible life — the sporting, the musical, the scientific, and the literary would have all featured.

Ushma S. Neill