Interviews

David Leslie and Naveed Sattar share insights into their careers, research, and the future of the diabetes field. Covering fascinating topics including autoimmunity and cardiometabolics.

Featuring: David Leslie and Naveed Sattar

David Leslie

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Q1 How did you first become interested in a career in medicine, specifically in your specialism in diabetes and autoimmunity?

I became interested in medicine because I loved biology, particularly human biology. I would have liked to have done genetics, but it seemed to me that genetics was not very well developed at that stage. At that point, colleagues of mine said to me, "David, you're not going to study snails, are you?" And then I thought the lack of acknowledgment and reputation if I was studying snails compared to being a doctor was not appropriate. I didn't hear angels singing or anything like that, there were no choirs! I was just very interested in biology. I was very unsure as to what to do.

I really wanted to do cardiology but in those days, which was back in the 1970s, there were literally no jobs, and I mean no jobs. I can remember at that time, that the President of the European Society of Cardiology (ESC) was aged about 43 and still a senior registrar; Douglas Chamberlain, whom I later worked with. It just seemed crazy, but there were just no jobs.

I then applied for two jobs, one which everyone thought I would get in chest diseases, and the other at King's College Hospital, London, UK, in diabetes, as King's was considered the best place to go for this. No one thought I'd get the job at King's because there was a very good candidate who was much more senior than me,

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but in the event, I got on enormously well with the person who ran the department, David Pyke. David became my colleague, mentor, and friend, really a father figure. And really, that was that. The decision as to whether I did chest diseases or diabetes was actually out of my hands because the interview at King's was one hour before the interview at the Royal Brompton Hospital, London, UK. I was dead certain that I would get the job at the Royal Brompton Hospital, but not at King's, but, I went to the King's interview, they offered it to me, and they said, "you have to make up your mind now!"

Q2 You were the first clinician to report many things; for example, early environmental events as a cause of Type 1 diabetes, early glucose changes during pregnancy being associated with congenital malformations, and persistent changes in the immune system as a predictor of diabetes. How does it feel to have been so instrumental in your field, and to have positively changed diabetes diagnosis and care for so many patients?

I love the excitement of discovering things, but no one discovers it entirely by themselves. Every single thing I've done has been with other people, and everything that I've done was just a race as to who got there first! I remember the early environmental story that I did with the late Bob Elliot, a New Zealander; he had the data, and I had the ideas. I said to him, "why don't we look at all of your data and see when these guys are developing this particular protein (an autoantibody)?" And he said, "oh, that's an interesting idea," and that was it. Most got the autoantibody before they were aged 5 years, so we wrote our paper up. I think that's pretty typical of all these things; you're never by yourself, always with people. At the end of the day, it's just a question of how much you try and claim it as your own, and whether you got there more or less first.

Q3 You were the Principal Investigator for three studies: Blueprint Epigenome, Action LADA (Latent Auto-Immune Diabetes in Adults), and EXALT. Could you tell us briefly what these studies are looking into, and why this is important in diabetes and autoimmune disease care and understanding?

Well, these are all European Union (EU)-funded studies, so that has a certain cachet. I was indeed the principal investigator for these three studies. The first one, Action LADA was about latent auto-immune diabetes in adults (LADA), and followed from the idea that there might be people in adult life who have Type 1 diabetes. Some people still think that Type 1 diabetes is a childhood disease, but the evidence is that adult-onset Type 1 diabetes is the most common form of presentation and it often presents in adults who do not initially require insulin. So, the most prevalent presentation of Type 1 diabetes is an adult with non-insulin requiring diabetes. That's where we are.

The Blueprint Epigenome study was awarded the largest sum of money ever given by the EU. It was about 30 million EUR to identify the so-called epigenome of the human body. To put it simply, my nose looks like a nose and my ear looks like an ear, but the genes are exactly the same genes. So, what's happened? And the answer is epigenetics; certain genes in my ear are switched off, and others switched on. That's epigenetics.

Some people say the difference between identical twins is epigenetics. It's the way a gene is expressed. There are lots of little markers put on these genes and they are expressed in different ways, and that's what we're doing. We published a number of papers on the subject. It's a fascinating subject. It's just in its infancy stage and there's going to be a lot more to come, too. I was interested in identical twins, which is what we used for that programme, and I was particularly interested in why one twin had diabetes and the other did not, even though they were identical

genetically. The implication was that it was a sort of epigenetic difference, and I suspect there is and that's what we're going to find one day. We're still analysing our data. The third EU grant was for immune therapy, which was an attempt to use a form of immune therapy to change the process of Type 1 diabetes. We did an initial early phase study, then a Phase IIa, and right now we're doing a Phase IIb study, where we're giving the treatment to people with recently diagnosed Type 1 diabetes to see if we can modify the disease process. If it works, we'll start looking at people at a very early stage of diabetes, perhaps even before they develop clinical diabetes because we can now predict the disease very well, even before the onset of clinical symptoms of diabetes.

Q4 Looking at professorships you hold, you're an Emeritus Professor to both Central South University in China, as well as a Chair at the University of Rome in Italy. In what ways do these positions aid your research, and the research carried out within these institutions?

I'm an Emeritus Professor in China, so I do a lot of work there. But in Rome, I'm the lead Professor of the International Medical Faculty. I've had a long association in Rome, and the person in charge of the department there also works with me in London. I enjoy this international collaboration; it's always been exciting, and they have a fantastic university set up both in China and in Rome. In Rome, we are promoting Italy's first English language-based medical course, and so that's been very entertaining. The engagement with China was for a more intellectual reason, because the incidence of Type 1 diabetes is highest in Northern Europe and lowest in China. I was interested in whether that difference is likely to be either genetic or environmental. It turns out that China does have a lower frequency of classic adult-onset Type 1 diabetes than we do in Europe. Globally, Northern Europe is the exception with its high disease incidence, not the rule. The reason Northern European children have a very high frequency of Type 1 diabetes is probably genetic because here we have a lot of high-risk disease-associated genes, but in the rest of the world, where they have low-risk genes or moderate-risk genes, it's not so high, and that's why there is this differential.

When it comes to more slow-onset disease, those presenting with non-insulin requiring Type 1 diabetes, that disease form is almost as prevalent in China as it is in Europe. I think in Europe, people who are diagnosed at a young age with Type 1 diabetes have a strong genetic component, but the older you are, the less genetically determined the disease. That observation is in line with what we found in identical twins. We found if you were diagnosed, as a twin, when you were young, let's say under the age of 10, then about 50–60% of your co-twins develop the disease, but if you are over 15 years of age, then only about 10–20% develop the disease. There's much, much less penetrance of the disease genes as you get older.

Q5 As an educator, where do you believe your focus will lie in the future?

My focus is increasingly turning to things beyond my future. I'm not looking to progress. I think my colleagues would be horrified if they thought that I was looking to hang around for 20 years or more. I think really when you reach my age, you're more interested in trying to help people develop themselves rather than yourself. With that in mind, one of the things I really am proud of is setting up a consortium called T1DUK, which is a consortium of the top research workers on Type 1 diabetes in Britain. Initially, only a few people joined me, and then gradually everyone joined in. We have this fantastic network now around Britain, with the T1DUK Consortium involved, not just in developing trials to try and prevent Type 1 diabetes, but also in developing ways of trying to expand our knowledge of the disease, and I'm really proud of that. And I think that's what guys of my age should be doing, looking to help other people. These guys in T1DUK are doing fantastic things, I mean, much more as a group than I could ever have done as an individual.

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Q6 What new advances in diabetes management are you most excited about and why?

I suppose we assume that there are two main types of diabetes, Type 1 and Type 2, but actually, I don't think there are two main types. I think there are many types of diabetes, so I think there's huge heterogeneity. This disease in children is different from the disease in adults, and that is true for Type 1 diabetes and for Type 2 diabetes. Some people with Type 2 diabetes are young and thin when they're diagnosed; others are older and obese. Only recently have we come to appreciate these differences. As we do so, we will start understanding that there are different ways you can treat the disease. I'll just give you one example: the standard treatment of Type 2 diabetes is metformin but actually in people who are under the age of 25 when they're diagnosed with Type 2 diabetes, 50% of them respond to metformin, whereas about 88% of older people respond. These are the sort of differential assessments that we're going to have to start understanding, appreciating, and coming to terms with, because suddenly we've got a lot of drugs available to us. And in the same way, we're now looking to maybe apply that sort of heterogeneity to Type 1 diabetes, as the therapy you use might be different in those who are very young compared with older-onset cases.

Q7 How has the COVID-19 pandemic affected your career in the field of diabetes research, and have there been any unforeseen benefits to this?

No unforeseen benefits whatsoever, apart from the fact that I think hybrid meetings have definitely got some value. I think the value is constrained by the fact that there's no dialogue. Even with us here, I'm answering your questions, but we're not actually having a dialogue, and I think that's true of all these virtual calls; they curtail dialogue. In terms of the future, it's dialogue that counts because it's that casual discussion in the pub or in the coffee shop that actually leads to better things. On the other hand, in terms of where we are at the moment, it's fantastic to be able to look at a talk that you would have missed if you'd been at the meeting, go back to it and look at the slides, to think about it in more detail. The hybrid presentations are great for the present, for learning where we are right now. But they're hopeless for looking into where we're going in the future.

Q8 What advice would you offer to someone considering a career in the field of diabetes and autoimmunity?

They need to decide if they're going to be an academic or not. If you're going to be an academic, then I think it's a very interesting and exciting field, and I think it's got a great future because there are so many unanswered questions. The thing that makes diabetes exciting is the fact that it's so prevalent. Most people by the age of 80 are either at risk of diabetes or have it, and it's going to get worse; that's just the reality. Diabetes is a condition with severe consequences, in need of better management, and for somebody that wants to do medicine, that's a very exciting prospect. I believe that the study of diabetes has always been a very academic sort of subject, really. A great area to go into if you are interested in making discoveries and making a difference.