We must maintain atmosphere

Jonathan Henderson: Tell me about the Bedford survey in the 1960s, which I think greatly enhanced our understanding of diabetes.

Professor Harry Keen: When I came back from the United States it was to Guy’s Hospital because I was invited to join the unit of Professor Butterfield - Lord Butterfield as he became - and it was there that the idea of the Bedford survey was born. It fascinated me because it seemed to be a wonderful opportunity to look at what you might call diabetes ‘in the raw’ in the population. The idea was to screen the whole adult population of Bedford to look for undiagnosed diabetes. In the 1960s notions about diabetes and its complications were still pretty primitive. It wasn’t very clear exactly why people with diabetes got problems with their eyes, kidneys, arteries. These things had not really been looked at on a population basis in a systematic way.

So the notion was to screen the whole of the adult population of Bedford by carrying out a collection of urine samples. We asked people to pee into a little pot, one of those small marmalade pots you get at hotels and on trains, and label it with their details, including whether or not they had diabetes, and put the pot in an envelope and leave it at the front door. The Bedford boy scouts, the guides, the Round Tablers, the Women’s Institute... all helped with the collection, delivering them to the local clinics where we had teams of people testing them.

We received a 72 per cent response from 40,000 adults, although some of them contained surprises. A lot of people could not bring themselves to put urine into their sample pot and so left them empty; some people thought it was an appeal and put money into the pots; and one wag put sherry into his pot. It was John Butterfield who was clever enough to say ‘This looks funny’, take the lid off, sniff it, put his finger in and taste it. And indeed it was sherry. We went to the person’s house and he agreed he had been pulling our legs and we finished up the bottle of sherry with him.

JH: What happened as a result of Bedford?

HK: We learnt very early on that a lot of people with diabetes got problems with their kidneys, arteries. These things had not really been looked at on a population basis in a systematic way.

A lot else happened as a result of Bedford. It showed us, for example, that a number of people had intermediate blood sugar levels that were a bit too high to be normal but not really high enough to have diabetes. For this quite large category of people, Bedford led us to invent the term ‘borderline diabetic’, which eventually became impaired glucose tolerance (IGT). That new concept of what might be called prediabetes fed into the WHO Expert Committee on Diabetes, which I chaired in 1979, and led to a whole new redefinition of diabetes on the basis of blood sugar levels, under reasonably standard conditions, that essentially still holds universally today.

Bedford gave us the chance to study the earliest appearance of kidney disease in people with diabetes. We recognised clinically that patients had got this complication when their urine went positive for tests for protein but by that stage the urine protein was already way up. With Bedford, we wanted to look at what you might call the blind area, when the urine protein leak has just started, often years before the level became clinically positive. So in the 1960s a colleague, Costis Chlouverakis, and I started looking for a way to measure very low but slightly increased quantities of albumin in the urine. A couple of then-young researchers called Nick Hales and Philip Randall had just developed a brilliant new method of measuring the very low levels of insulin in plasma using two antibodies so we decided to adapt their method for albumin in urine. Within two
of enquiry and research

weeks we had developed the test for human albumin in urine and within months we had described microalbuminuria [the passage of very small excess quantities of albumin in the urine]. Using this technique, in the 1970s, my colleague GianCarlo Viberti made some really breakthrough observations on early diabetic kidney disease. It took at least another 10 to 15 years to persuade the Americans of its usefulness, but microalbuminuria is now internationally recognised as a standard indicator of the very earliest signs of diabetic kidney disease and also, rather remarkably, of cardiovascular disease risk.

Another new insight that came out of Bedford was that we showed for the very first time on a population basis that there was a relationship between the degree of glucose intolerance and the increased risk of developing coronary heart disease and cardiovascular disease generally. We showed the relationship cross-sectionally at the time we first conducted the survey and in terms of incidence when we looked again five years later. My colleagues John Jarrett and John Fuller have subsequently built much additional understanding of the epidemiology of diabetic complications.

**JH: Tell me how you invented the pump.**

HK: When I was at King’s College Hospital, Dr Robin Lawrence told me that his patients who did best were those on multiple small doses of insulin, so I figured that the nearest you could get to a real multiple dosage was to give a continuous but variable infusion of insulin under the skin. Colleagues at Hotel Dieu in Paris had looked at continuous infusion of insulin into a vein but this was fraught with hazard. They could only run it for two or three days because of veins clotting or bloodstream infection. It struck me that if you could infuse the insulin under the skin in very low volumes you would eliminate those hazards. The first person to try was one of my patients (Mrs Winifred Vincent) who had been admitted to the ward because her diabetes was so badly controlled. Using an ordinary syringe mounted on a Harvard syringe driver by her bedside, insulin was slowly pumped in under the skin through a fine catheter. The response of her blood glucose was spectacular - and the rest, as they say, is history. Her dramatic blood glucose improvement led me to suppose there really was something quite powerful here.

What I needed was obviously a much smaller device, a pump that the patient could carry around with them. A colleague told me that a chap called John Parsons was using a miniature pump to infuse parathyroid hormone into rats at the National Institute for Medical Research at Mill Hill. We brought his little infuser, a few inches long, along to Guys and used it on a succession of patients. It was quite clear we had an exciting new approach to controlling type 1 diabetes and my young colleague John Pickup really picked up the pump and ran with it. His industry, enthusiasm, ingenuity and initiative led to its full development.

**JH: What is the most promising type 1 research going on at the moment?**

HK: There are two major lines we have to look carefully at: one is cure, the other is prevention. So far as cure is concerned the best bet for getting as near to a cure as one can is the replacement of islet of Langerhans cells, the tissues that make insulin, which have been irreversibly damaged. One of the major problems here is access to enough of the islet tissue needed for the grafts. What may help is being able to get islets of Langerhans from pigs or other animals genetically modified so that humans don’t reject their tissues. This would make it possible to restore normal blood glucose levels in much larger numbers of people. Life without injections and insulin reactions would be much more acceptable and the risk of diabetic complications greatly reduced or eliminated.

**JH: Are you excited by the work being done with stem cells?**

HK: Very and I would put a lot of resources and energy into exploring them. They are the elephants in the diabetes room at the moment. There’s a sort of hush of expectation that something is going to break through at some point but who knows who, what or where? The classic scientific unpredictability principle is at work here. The one thing you can be sure of is that if we don’t work at it then nothing will happen. Only if we do get to work will someone at some point make the breakthrough. The nub of the scientific question is how you can persuade undifferentiated stem cells to turn into respectable, responsive insulin secreting islet cells. The first steps have been taken but creating fully active and reactive islet cells still lie in the future.

**JH: Do you think that prevention is ahead of the cure?**

HK: I do. They are both terribly important but I think that prevention probably holds out a better prospect at the moment because we know so much more now about the sort of person who is liable to get type 1 diabetes. We know quite a lot about their genetic makeup and we can detect some of the very first manifestations of the destructive process that is eventually going to knock out their beta cells. What we still do not really understand is what initiates it. Some of the evidence suggests that in some cases it may even start during development in the womb, before birth. One of the things that has become quite clear is that the clinical appearance of diabetes is the end of a process and not the beginning of it - and it’s the end of quite a long process, months or even years during which there are probably waves of attack on just the beta cells. It’s likely that some recovery with new cell formation happens after each attack until the islets finally run out of replicative potential and diabetes appears.

There is much that we know that will be translated into what we can do to prevent the type 1 diabetes but in the meantime there is a great deal that we both know and can do in the prevention of its complications. All of our clinical effort and much of our clinical research effort should be going towards trying to help the person with type 1 diabetes get improved control of blood glucose while reducing the burdens of treatment and the risk of hypoglycaemia.

Of key importance is maintaining the atmosphere of enquiry and research. In collaboration with many very able colleagues, I have enjoyed the privilege of combining an active investigative career with the care of patients and teaching. I could wish no better future for a young person embarking on a life in medicine.

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