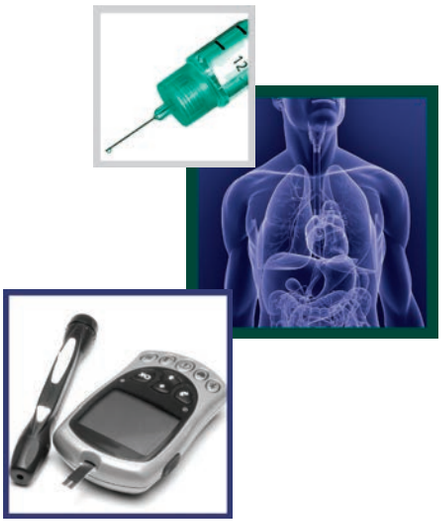

The cause of Type 2 diabetes: a new paradigm

Paul Zimmet[†]: Professor Paul Zimmet was the Foundation Director of the International Diabetes Institute, which merged with the Baker IDI Heart and Diabetes Institute in 2008 to create the largest diabetes and cardiovascular disease institute in the Southern Hemisphere. He is co-chair of the International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention. He is also the Director Emeritus of the Baker IDI Heart and Diabetes Institute (Melbourne, Australia). Professor Zimmet served on the Australian Government Executive Committee for the Prevention of Type 2 diabetes and since 2008 has been involved with the Australian Labor Government's Prevention Taskforce for Obesity, Tobacco and Alcohol. Numerous awards have been given in recognition of Professor Zimmet's work, including awards from the American Diabetes Association, the European Association for the Study of Diabetes, Diabetes UK, the Australian Diabetes Society and the Canadian Diabetes Association. In 2007, he received the international Novartis Award for the significant impact that his research has had in the field of diabetes and in 2010 he was the recipient of the prestigious Grand Hamdan International Award for Medical Sciences in the field of diabetes and joined a small select group as Honorary Life Member of the European Association for the Study of Diabetes. Professor Zimmet has published over 700 scientific papers, along with several book chapters.

Q Could you briefly summarize your professional background to date?

I started out by training as a clinical physician in the field of diabetes; however, my mentors convinced me that I should consider doing a PhD. I ended up doing a PhD in Biochemistry at Monash University (Australia) followed by post-doctoral work at Guy's Hospital (UK). This was focusing on the field of diabetes. Here I worked with Professor Harry Keen, who convinced me that it would be a much more interesting life to combine the clinical role with epidemiology. So it was at Guy's Hospital that I got into the main areas that I am now recognized for. Over time I have ranged right through from being a clinician who sees patients, through to the laboratory, and I have also been very much involved in public health and epidemiology both in diabetes and obesity.

Q How did you first become interested in the field of diabetes?

Whilst working in Melbourne (Australia) I sort of fell into the field by accident. I was keen to stay in the city so I applied for one of the only jobs I could see available, as a diabetes registrar. I got the job. In this

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role, we were very interested in the area of diabetic ketoacidosis. I became interested in a study examining what constituted acidosis, and what metabolites might be involved in causing the acidosis. At the same time I became involved in a study relating to a woman with tetany; during this study I discovered the cause was magnesium deficiency [1]. This discovery fired up my interest in clinical research and being involved in endocrinology. I just continued in the area.

Q Were there any particular colleagues who you worked with that had an influence on the path that your research has taken?

I did my PhD under Professor Bornstein, who was the first to demonstrate the biochemical difference between Type 1 diabetes (T1D) and Type 2 diabetes (T2D). He developed the first bioassay for insulin, and showed that most of the mature-onset diabetes patients did actually have insulin. Nobody in Australia believed him, so he came to London to King's College. Here he worked with Robin Lawrence. In 1951 they published an article in the *BMJ* differentiating the two forms of diabetes [2]. Yalow and Berson developed an immunoassay for insulin 10 years later and they won the Nobel Prize for demonstrating the difference between T1D and T2D. I worked with Bornstein after that time, during my PhD in the 1970s. He was an inspirational guy.

Later I came to London, and worked with Professor Harry Keen at Guy's for a year and a half. He had the biggest influence on my career. As I mentioned before he got me interested in epidemiological studies. When I went back to Australia I followed through with this path. I went on to do a survey on the Pacific island of Nauru and demonstrated the highest rate of diabetes in the world [3].

There are other people who I feel have been very influential in my career, for example, Dr Peter Bennett who headed up the Pima Indian studies [4]. Before I discovered the high rate of diabetes in Nauru he had demonstrated that the Pima Indians in Phoenix (Arizona, USA) had the highest rate of diabetes in the world.

Another person who has been very influential is the current President of Diabetes UK, George Alberti, who I have worked consistently with for the last 30 years on various projects. We have worked together for the WHO and the International Diabetes Federation. We are currently co-chairing the International Diabetes Task Force (IDF) on the epidemiology and prevention of diabetes, as part of this we have produced very important mission statements for the IDF and we will be producing another one shortly on the use of bariatric surgery in the treatment of obesity in T2D. Recently, there has been a move towards surgery for the treatment of very obese people with T2D. In many instances they would get what we would call 'a cure for the diabetes' quite independent of the weight loss. This procedure has become very popular and is now frequently undertaken, despite the fact that there are no international guidelines in terms of patient selection, the surgical procedure that should be undertaken, the follow-up of the patients and the type of team that is needed. The IDF is putting out a statement to give international guidance on this approach.

Q What do you consider to be the biggest achievement in you career so far?

I think there are two things that stand out for me. The first is that I established the first institute in Australia for diabetes that not only covered clinical care and education, but also research covering basic genetic and laboratory research through to epidemiological studies. I couple this with that the fact that, I think it is fair to say, people 'blame' me for successfully predicting the epidemic of diabetes, which is now one of the biggest epidemics now in human history. I came up with this prediction in the late 1970s because when we were working in the Pacific islands and in Nauru we discovered the highest rate of diabetes in any population in the world (33% of the adult population are affected). We then studied eight other island communities including Samoa, Cook Islands and Papua New Guinea, which did not have quite such high rates, but it was quite clear then that there

was going to be an epidemic of diabetes in far greater numbers than anyone had ever expected. No one believed me for a while. Now everybody accepts that it was our research that predicted what was going to happen. I was thrilled to receive the prestigious 2010 Grand Hamdan International Prize in Medical Sciences for those studies.

Q Why is the percentage of people with diabetes so high in the Pacific islands?

We used to believe that these people had a very high genetic susceptibility; we used the concept of the thrifty gene hypothesis. The Pacific islands were subject to periods of feast and famine; people living there had the gene that allowed them to store food during the feast period for times of famine. These days, with food aplenty, the storage gene results in obesity and insulin resistance with T2D. However, we now believe it is a much more complex issue.

Another person who has influenced my thinking very much over the past few years is Peter Gluckman, the Prime Minster's Chief Science Advisor in New Zealand, who is a very firm believer and proponent of the idea of maternal nutrition (i.e., what the mother eats sets the baby up for adult diseases such as diabetes and heart disease). We believe that many regions of the world have gone through these times of famine where we see high rates of diabetes. For example, China and Cambodia went through periods of very poor nutrition and famine, and mothers who delivered babies at this time, delivered babies whose genetic material changed to such an extent that in their adult life they developed diabetes, heart disease and obesity. It is a distillate of the Barker hypothesis.

Q What is the largest project that you have worked on?

There are two very large projects that I have worked on. One is the national Australian diabetes study called AusDiab, which I designed and established. We are just about to carry out our 11-year follow-up study, looking at the patterns of diabetes in Australia (for the original study see [5]). Another big project that I have been involved in is the Mauritius project, where I have been looking at diabetes and heart disease since 1987. We have had five surveys in Mauritius, the most recent being in 2009 [6]. We have shown that in the community, which has three ethnic groups, Chinese, Asian Indians and Africans, there has been more than a 60% increase in diabetes over the last 20 years, similarly across all ethnic groups. The importance of Mauritius is that those three ethnic groups represent the ethnicities that constitute two-thirds of the world's population. Therefore the study provided additional support to our hypothesis that there was going to be a global epidemic. This is because what happened in Mauritius was then mirrored in China, India and Africa, where diabetes has been escalating.

Q Could you elaborate on your involvement in the Australian Government's diabetes programs?

In 1986, I was one of two people who convinced our new Minister of Health at the time, Dr Michael Wooldridge, that diabetes was very important. This triggered an interest in diabetes within the Australian Government, which has only increased with time. I was on the original official Ministerial Advisory Board (there were only three or four of us), advising the Minister on various diabetes programs in terms of guidelines, programs for gestational diabetes, prevention initiatives and what drugs were needed. Subsequently, owing to the AusDiab results showing how high the number of diabetics was in Australia (over 1 million), I was involved in a government committee to help develop programs for T2D prevention. In more recent times I have been on the government's Preventative Task Force, which was established in 2009, advising the government on the prevention of diabetes through the effects of alcohol, diet and tobacco.

At the moment I am in a government group called the Diabetes Advisory Group (DAG), which is involved in advising the government on the implementation of diabetes coordinated care plans for primary healthcare. The DAG group is currently advising the government on a pilot project, which, if successful, will then be rolled out through the country and GPs will be given funds to direct patients to various allied

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healthcare professionals, such as dieticians and educators, podiatrists and psychologists for any specific diabetes-related needs. There has been much written and published on the team approach to diabetes management with the patient as the central figure – this plan is maybe one of the first in the world where a national program is being established. It has not been rolled out yet, but at least there is a major pilot to test whether it really is feasible.

Q What advances do you expect to see in the field of diabetes over the course of 2011?

The research in T1D seems to move very slowly. I would like to hope that by the end of this year we can say that we know what causes T1D. This will then mean that we may establish the best prevention approaches. The current strategies are very much 'bunderbluss shotgun' approaches as we really do not know what causes T1D. To discover what the cause might be within 12 months is a real challenge.

Type 2 diabetes is easier to manage, in that lifestyle measurements can prevent T2D in up to 60–70% of people. The only problem is that it is very hard to convince people to change behaviors! Maybe we will make some progress in understanding those psychological and behavioral approaches in that area.

There is now very strong epidemiological evidence that a major driver of T2D and obesity epidemics is what happens during pregnancy, the effect of both the environment and the mother's behavior on the fetus. I would like to see governments accept this, even though we do not yet have the final evidence, so that they can start looking at the long-term approach and start working on maternal and childhood programs and evaluating them to see whether in fact we can turn the epidemic around.

Another area where I would like to see a lot more action is research into why mothers who develop T2D in pregnancy give birth to children who are more likely to get T2D in adult life. We seem to have an intergenerational theme, that becomes a vicious cycle. We need to look much more closely at this issue of pregnancy and the management before, during and after birth. We may have missed this key fact in the last 20–30 years with our belief that slovenly and sedentary lifestyle along with poor diet is the main reason for T2D. We have a lot of ground to catch up on. I think we potentially have the wrong paradigm in thinking, 'what causes T2D?'. I am hoping for quite a shift in our outlook in the future.

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Financial & competing interests disclosure

P Zimmet has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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