



Paul Zimmet: A Voice for Diabetes

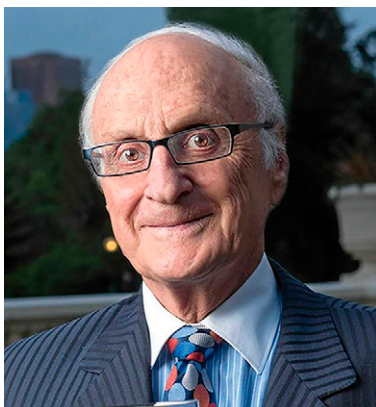
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Paul Zimmet has been one of the leading figures, globally, in transforming the understanding and threat of diabetes from a Cinderella disease to a major plank of most governments' health policies. His science, particularly a series of epidemiological studies, has been at the forefront of the campaign, but it is fueled by his genuine passion to improve the life of people with diabetes. After more than 50 years of working in the diabetes field, he continues to actively push the boundaries of our understanding of the condition.

The Zimmet family has medicine running through its veins, but it was not always the somewhat privileged life of the professional classes. Paul Zimmet's father, Jacob, was born in Tarnopol, Poland, and graduated in medicine from the University of Vienna in 1935. However, with rising anti-Semitism, the only position available to him was an unpaid one at the Tarnopol Hospital. Jacob realized there was no future in Poland, and in 1938, he, along with his wife and first child, Rena, fled Poland and fortunately was able to obtain passage to Australia. Of all the family that remained behind, only one survived the Nazi concentration camps. Australia was far from the horrors of the Holocaust, but life was still not easy, as Jacob had to requalify in medicine, which he achieved at the University of Adelaide in 1942.

Paul was born in 1941 and grew up in his father's country medical practice in Whyalla, a small town nearly 400 km from the city of Adelaide. From such small beginnings, a dynasty of medicine began, as Paul, two of his siblings Rena



Paul Zimmet

and Leon, Paul's two sons Hendrik and Marcel, and Paul's nephew Adam entered the profession, and between them have specialized in diabetes, cardiology, pediatrics, and cardiac surgery.

Paul graduated from the University of Adelaide in 1965 but moved to Melbourne to start his clinical work at the Alfred Hospital. It was in Melbourne that he met his wife, Vivien. Vivien has accompanied Paul and participated in field trips and on conference travel and, indeed, has been a wonderful partner and inspiration during his career, enabling him to translate his vision and research into action.

In 1967, Paul was offered the position of Diabetes Registrar in the Alfred Hospital's Diabetes and Metabolic Unit and also had his first of more than 1,000 publications. As with many great scientists, a casual observation, which most people would ignore, led to an important insight. An inpatient with hypocalcemia and tetany was

unresponsive to calcium replacement. While half listening to the "Farmers' Hour" on the radio, Paul's ears pricked up when the discussion turned to magnesium as a treatment for grass tetany in cows. After then checking the patient's serum magnesium, and finding it to be very low, magnesium replacement cured the hypocalcemia and the tetany, and the *British Medical Journal* published the report (1). The journey of curiosity, investigation, and dissemination had begun.

Paul's academic career began in earnest in 1970, when he commenced a PhD at Melbourne's Monash University with Professor Joe Bornstein. Joe had previously developed one of the first insulin bioassays, which he used, along with R. D. Lawrence, to demonstrate that there were two types of diabetes, differentiated by the absence or presence of circulating insulin. Paul's PhD focused on two growth hormone fragments as potential contributors to glucose regulation in type 2 diabetes, one of which entered clinical trials as a potential drug for diabetes 35 years later. However, Paul believed he needed to take his work beyond the bench and into the field of epidemiology to understand its significance and so took up a postdoctoral position in London's Guy's Hospital with Harry Keen and John Jarrett, two of the great pioneers of diabetes epidemiology. While he was in London, Paul came across the work of the leading New Zealand epidemiologist, Ian Prior, who, in a 1966 paper on gout, also reported an elevated prevalence of diabetes in New Zealand Maori and in

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another Pacific Polynesian Island population (2).

The diabetes findings were hardly prominent. The diabetes data did not make it into any of the nine tables or five figures, but Paul spotted them, recognized their significance, and on the basis of this, began his seminal descriptions of the diabetes epidemic in the Pacific.

Returning to Australia from London, he convinced his previous boss, Pincus Taft, who had a clinical link with the President of the Pacific Island of Nauru, to establish a diabetes survey on this remote island. Since the discovery of phosphate on the island, Nauru had, by the 1970s, achieved the highest per capita GDP in the world. Profound lifestyle change had dramatically altered the diet and the physical activity levels of the small population. Out of 100 people recruited on the first day of the survey, 33 were found to have diabetes. By the end of the survey, the prevalence of diabetes was recorded as 30% (3), the highest national prevalence ever reported. Paul famously presented the data at the 1976 European Association for the Study of Diabetes (EASD) meeting wearing a bright red safari suit purchased in London en route to Helsinki for the event. He wanted to be noticed. He wanted the message to be noticed. He had started his journey to tell the world that diabetes was becoming a global health threat.

The World Health Organization (WHO) asked Paul to conduct similar surveys in other Pacific islands. While Nauru remained the standout for diabetes prevalence, every other island had a high diabetes prevalence. These other islands included Fiji, New Caledonia, the Cook Islands, Kiribati, Tuvalu, and Western Samoa. His research was supported by the National Institutes of Health for over 20 years, and Paul became one of the longest continuously funded National Institutes of Health researchers outside the U.S. Paul was also invited to visit and provide a WHO report on what was suspected to be an emerging diabetes and cardiovascular disease problem in the Indian Ocean island of Mauritius in the 1980s. This led to him teaming up with long-term collaborators George Alberti and Jaakko Tuomilehto, and later with myself, as we described the epidemic of

diabetes gripping Mauritius. The ethnic mix of the population of this island (derived from India, Africa, and China) allowed inferences to be made about the likely global reach of the diabetes epidemic. Multiple subsequent studies in India, in China, and in the Indian and Chinese diasporas around the world confirmed Paul's predictions that epidemiological transition was making diabetes into a global health threat. More than 30 years later, Paul remains closely involved with advising the Mauritian government, and the diabetes-focused health surveys continue, in one of the longest series of national diabetes surveys anywhere in the world.

Behind the "headline" population prevalences and the bright red suit was careful research that was teasing out the influences of lifestyle and ethnicity on the risk of type 2 diabetes and describing the transition rates from normal glucose tolerance to impaired glucose tolerance and diabetes. The island populations presented a series of "natural experiments" in which subgroups with varying exposures to putative diabetes risk factors could be studied for their prevalence of diabetes. These lifestyle and anthropometric risk factors are now standard textbook material, but Paul was among the pioneering epidemiologists who developed the hypotheses and assembled the data. Furthermore, he recognized the need to move the findings beyond the realms of academia. He believed, rightly as it turned out, that what he was describing in remote island nations was about to hit the rest of the world. He borrowed phrases like "Coca-colonization" from authors like Arthur Koestler and the political and social sciences (4) to draw attention to the perils of lifestyle change, thereby ensuring that his message was heard by the media and by governments. For the last 20 years, the International Diabetes Federation has produced estimates of the global burden of diabetes, and projections for the future, as it recognizes the need to have appropriate data to demonstrate the importance of diabetes and to drive policy change. But Paul did it first. His global and country-specific estimates of diabetes prevalence for 1995 and projections to 2010 (5) set the scene for others to follow. It was a perfect

example of the nexus of epidemiology and science with politics and action.

The data collected in the epidemiological studies also proved to be ideal for understanding the implications of the changes in diagnostic criteria for diabetes that were instituted in the late 1990s. I was fortunate enough to join Paul as a research fellow just at the time that the WHO (whose Diabetes Expert Committee Paul cochaired with George Alberti) and the American Diabetes Association were lowering the fasting glucose diabetes cut point from 140 to 126 mg/dL (7.8 to 7.0 mmol/L), and the American Diabetes Association was de-emphasizing the role of the oral glucose tolerance test and popularizing the use of the term "prediabetes." Together we were able to show, in a series of papers across the multiple ethnic groups represented in the various island surveys, how diabetes phenotype differed according to diagnostic criterion (6). This provided the model for similar analyses a decade later when HbA_{1c} was introduced as a diagnostic criterion.

The late 1990s saw Paul's research attention focused finally on his home country of Australia. Along with Tim Welborn, he persuaded both federal and state governments to provide funding to conduct the first ever national diabetes survey, the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) (7). With >11,000 participants, this became the largest national survey to use an oral glucose tolerance test, was critical in forming Australia's national diabetes policy, and, 20 years after its inception, is still producing high-quality publications. During this period, Paul and I became productive collaborators, forming a very strong and lasting scientific partnership and personal friendship. The results from AusDiab had a profound impact on recognizing the significant impact of diabetes and its associated complications and comorbidities in the Australian community. The outcomes provided ample evidence of the urgent need for preventative action against the growing burden of type 2 diabetes in Australia. Importantly, AusDiab also provided a platform for David Dunstan, one of Paul's postdoctoral fellows, to establish some of the earliest findings about the contribution of sedentary behavior (separate from exercise) to

cardiometabolic health (8). Subsequent work by David, and others around the world, has now led to relevant recommendations in guidelines worldwide.

Paul's work mainly focused on the epidemiology of type 2 diabetes, as this was critical in understanding the global epidemic. But grass tetany and hypomagnesemia were not his only forays outside this arena. Paul worked with the late renowned Ian Mackay in Melbourne and developed what was arguably the first immunoassay for GAD antibodies. Then, in collaborations with Leif Groop, Tina Tuomi from Finland, and others, the value of islet cell autoimmunity for characterizing people who were diagnosed with type 2 diabetes, but had very poor insulin secretion and rapidly progressed to insulin therapy, was established (9). Latent autoimmune diabetes of adulthood (LADA) was defined, and the anti-GAD assay became a critical and widely used clinical tool in differentiating autoimmune type 1 diabetes from type 2 diabetes.

A joint study in Finnish women with Jaakko Tuomilehto then clearly demonstrated the predictive value of anti-GAD, showing it could be detected up to 15 years before the later onset of type 1 diabetes (10). With Professor Robert Turner (Oxford University), at Paul's suggestion, Paul and Ian Mackay tested samples from the UK Prospective Diabetes Study (UKPDS) type 2 diabetes cohort. Ten percent of those classified as having type 2 diabetes were found to have type 1 diabetes based on positive anti-GAD serology (11).

Through Israeli colleagues, Paul had also become aware of a novel animal model of type 2 diabetes, *Psammomys obesus*, also known as the Israeli sand rat (it is actually a gerbil). It is lean and healthy in the wild in the Negev Desert but rapidly becomes obese and develops type 2 diabetes along with several features of the metabolic syndrome on a "Western diet" in the laboratory. Circadian disruption has also been shown to play a role in these changes. Paul worked with Greg Collier, at Melbourne's Deakin University, and they established a colony and produced a series of elegant studies (12) on the genetics and metabolic defects characterizing the metabolic syndrome.

Paul has had a long association with the metabolic syndrome and, with George

Alberti, Robert Eckel, and Scott Grundy, managed to achieve the seemingly impossible in uniting several major international societies behind a single "harmonized" definition of the syndrome (13). More recently, he has been working to advance the hypothesis that circadian dysregulation sits behind many of the features of the metabolic syndrome and has proposed the circadian syndrome, which incorporates the metabolic syndrome along with its associated comorbidities including depression, sleep apnea, and fatty liver (14).

While Paul's main activities have always been in research, he has also been a leader in clinical services. After visiting the Steno Memorial Hospital in Copenhagen in 1973 on his way back to Melbourne after his postdoctoral stint in London, he saw the importance of uniting diabetes care with training and research into a single entity.

The Steno visit, at the invitation of Jorn Nerup, provided the inspiration for Paul's vision to establish the International Diabetes Institute as an integrated center for diabetes research and care.

In 1985, Paul and physician-colleague Matthew Cohen established the International Diabetes Institute in Melbourne. It combined a large diabetes outpatient service and prominent diabetes education center with the research group that Paul had built up. The major influence domestically and globally of this one-stop shop for diabetes was recognized when it was designated as the first WHO Collaborating Centre for Diabetes.

Paul has also played a significant role in promoting improvements in Indigenous health. His work with high-prevalence Pacific Island populations, and his close association with Peter Bennett, who was working with the Pima Indian population, made this a natural extension. Within Australia, health outcomes for people of Aboriginal and Torres Strait Islander origin have remained depressingly poor, with the high prevalence of diabetes being a key driver. Paul was instrumental in establishing an outreach diabetes education service from the International Diabetes Institute with the Indigenous community in Northcote, a Melbourne suburb. Later, when the International Diabetes Institute had merged with the Baker Institute to

form Baker IDI, he was involved in the development of a diabetes clinical service for remote communities 2,000 km away in Central Australia. A diabetes nurse education service was based locally in Alice Springs, and diabetologists swapped the city life in Melbourne for a week in the Outback and the desert to connect with communities, provide care to people with diabetes, and deliver education to health care professionals. Paul has also taken a keen role in promoting research into the challenges of diabetes in Aboriginal populations. He has strongly supported Alex Brown and Louise Maple Brown, two of Australia's outstanding researchers in this area, to improve both research and delivery of clinical care in Indigenous communities.

Paul's achievements have been widely and appropriately recognized by learned institutions the world over. He has honorary degrees, doctorates, and appointments from universities in Europe, North America, Asia, and Australia. Every major diabetes conference has honored him with awards, and the Australian Government recognized his contributions by installing him as an Officer of the Order of Australia. He has been featured on numerous lists of the most highly cited researchers in the world.

In Australia, Paul was co-chair of the 2016–2020 National Diabetes Strategy and was recognized nationally as the 2018 Senior Victorian Australian of the Year. His international and national awards include the Kelly West and Harold Rifkin medals (American Diabetes Association), the Kellion Victory Medal (Australian Diabetes Society), the Banting award (Diabetes UK), the A.M. Cohen Memorial Award and Lecture (EASD, Jerusalem 2000), and the Hellmut Mehnert/German Diabetes Union Award (EASD, Munich 2004). He received the Grand Hamdan International Prize for Medical Sciences (Dubai) in 2010 jointly with Jaakko Tuomilehto. Paul was particularly proud of receiving Research Australia's Peter Wills Medal in 2013. This award recognizes an Australian scientist who has made an outstanding contribution to building Australia's international reputation in health and medical research. Paul is also the only Australian to be made an International Member of the Royal National Academy of Medicine in Spain.

In a career packed with international research programs, a prolific publication output, frequent negotiations with governments, and the responsibilities of running an institute, Paul has still found time for individuals. Many of those who have worked with him, closely or at a distance, have benefited from his mentorship and his ability to provide opportunities and encouragement for the up and coming. He has faithfully provided care to his patients, many for several decades. But, above all, he has remained close to his family. Despite the challenges of running studies on Pacific islands, and the time required to travel from Australia to almost anywhere else, Paul has remained intimately connected with his family. It epitomizes his ability to care about the individual while dealing with the population.

Paul Zimmet has been a towering figure in the diabetes field for several decades. He has been a driver of the research agenda, has never been afraid to challenge the status quo, and has cajoled and harangued governments and influential NGOs into paying more attention to the diabetes epidemic. The world of diabetes would have looked very different without Paul Zimmet.

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