Bernard Zinman: A Canadian Clinician Scientist Changing the Management of Diabetes

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Bernard Zinman is one of Canada's leading diabetes clinician scientists, and his body of work has considerably expanded our knowledge of both type 1 and type 2 diabetes. The findings of his studies have resulted in major changes in clinical practice guidelines nationally and internationally, positively impacting the lives of millions of families.

Bernie was born in Montreal in 1943 to immigrant Jewish parents. At the turn of the century, his father, Abe Louis Zinman, came to Canada as a child from a small shtetel on the Dniester River, Ukraine (*Fiddler on the Roof* vintage). Abe attended public school in Montreal, and subsequently his family moved to the small rural community of Saint Jean in the province of Quebec, just north of the American border, to set up a scrap metal recycling business, which more than 100 years later is still functioning (Zinman Metals).

As a young man, Abe set out on his own and independently established a retail store in the same community of Saint Jean. The family of Dora Goldberg, Bernie's mother, immigrated to the U.S. from Poland when she was a child. As a young adult she came to Montreal for a family wedding and met her future husband, Abe Zinman. It was love at first sight. He was smitten by this beautiful, intelligent woman and continued a courtship, taking the night train to New York every weekend. They married and established a family in Saint Jean. Their first child, Saul, was followed by a second son, Albert, 10 years later, and 5 years later, despite their hopes for a daughter, Bernie arrived, the third son. The family moved to Montreal so the three boys could get a Jewish school education. Tragically, at the age of 43 Dora developed pemphigus, a universally fatal disease in 1951, and Abe became a single parent for Saul (age 23), Albert (age 13), and Bernie (age 8).

The four "men" established a home in a middle-class neighborhood. Abe's focus was on his youngest son, and he clearly had the greatest influence on Bernie's development. He would never remarry, as Dora was the love of his life and could not be replaced. Fiercely independent, he lived alone and was immensely proud of his three sons, their wives, and his grandchildren. Bernie quickly appreciated that his real interests lay elsewhere, beyond the retail and business world. His mother's ancestry and heritage, replete with rabbis and scholars, influenced him to seek higher education, and he was the first in his family to go to university. At McGill University in Montreal he enrolled in the honors biochemistry program, where he was introduced to the excitement of discovery science, and he subsequently went on to graduate from McGill Medical School, where he received his MDCM degree.

As a young medical student, he had the good fortune to be mentored by Charles Hollenberg, who provided excellent counsel and guidance. Charles

Hollenberg was subsequently recruited to the University of Toronto as chair of the Department of Medicine, which ultimately had a major impact on Bernie's future career choices. In his 4th year of medical school, a classmate introduced him to Jean Zucker, and they had their first coffee date; in just 6 months they were engaged and married, before Bernie started his internship. They rented an apartment close to the hospital so Bernie could be on call from home, and 13 months later their firstborn, Deborah (named after Bernie's mom), arrived. Lorne and Andrew soon followed, all three born in Montreal before they moved to Toronto. Deborah is a cofounder

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of an internet company, Lorne is an academic neurologist, and Andrew is a lawyer, all making Toronto their home.

Given his interests in biochemistry and metabolism, it was not surprising that Bernie gravitated to endocrinology. During his internal medicine training he completed a research program under the supervision of Richard Ogilvie, a clinical pharmacologist, employing forearm perfusion methodology to demonstrate that sulfonylureas had no peripheral insulin-like action and that their entire effects were due to β-cell insulin secretion (1). With their young family in tow, Jean, Bernie, and three toddlers headed west down the 401 highway to Toronto, where Bernie initiated postgraduate endocrine training supervised by Jack Laidlaw. His first serious research program was in the Hollenberg laboratory, evaluating the effect of insulin and lipolytic agents on a specific enzyme, rat adipocyte low-K_m cyclic adenosine 3′5′-monophosphate phosphodiesterase (2).

On completion of his endocrine training in Toronto, the Zinmans moved back to Montreal, where Bernie's first academic appointment was to the Division of Endocrinology at the Jewish General Hospital, McGill University. He established a basic science laboratory with Medical Research Council funding at the Lady Davis Medical Research Institute. Just 6 months later an attractive junior faculty position became available at the University of Toronto. Taking wise counsel from Jean, the Zinman family packed up again and returned to Toronto. This move also provided Bernie the opportunity, after some reflection, to refocus his research interests on clinical investigation. With Errol Marliss and Mladen Vranic as senior mentors and collaborators, a series of experiments defining the impact and role of acute exercise in type 1 diabetes were published (3,4). At the same time, he joined the artificial pancreas group led by Michael Albisser and explored the early metabolic impact of closed-loop glucose control (5).

I first encountered Bernie as a young medical student in 1977, when I started doing endocrinology electives at Toronto General Hospital. A few years later, I had the opportunity to study and write up the case of an interesting person with type 1 diabetes experiencing multiple sequential honeymoon remission periods. We managed to obtain quite a lot of dynamic testing, assessing levels of insulin and glucagon, throughout the course of the remissions and relapses. I remember when we received the first reviews, largely rejections, accompanied by pages of critical reviewer comments. I was devastated. Bernie, on the other hand, scanned the reviewers' comments, smiled, and quickly proclaimed in an optimistic manner "they like your paper, this should be no problem for us to get it accepted." I was bewildered and inexperienced, but Bernie's judgment proved correct, as the article was ultimately published in *Diabetes Care* (6). Subsequently, I went off to learn about the new developments in molecular biology and Bernie stayed focused on clinical investigation. In 1987, I found myself working with Bernie again, as a junior colleague in the Division of Endocrinology at the University of Toronto. Three decades after our first joint publication, I once again coauthored an article in *Diabetes Care* with Bernie, cosupervising an endocrine fellow, Julie Lovshin, in her studies interrogating the cardiorenal mechanisms of liraglutide action (7).

In the 1970s and 1980s, a debate raged among clinicians and researchers as to whether the long-term complications of diabetes were an inevitable, genetically determined consequence or related to imperfect or poor glucose control. A request for application was issued by the National Institutes of Health (NIH) to test the "glucose hypothesis," namely, that improved glucose control will prevent or slow the microvascular complications in type 1 diabetes. Recognizing this opportunity, Bernie was encouraged by Errol Marliss to respond to the request for application, and Toronto, under Bernie's leadership, was one of the original 21 centers funded to design a clinical trial to address the glucose hypothesis of diabetes complications. The group was led by Oscar Crofford, and with the aid of monthly meetings in Washington, DC, for a year (1982), the protocol and manual of operations were developed (8). The study needed a name, and Bernie won the naming contest, coining the acronym DCCT (Diabetes Control and Complications Trial), and as a prize was given a vanity license plate with a Canadian bent: "NIH EH?". Working with the study coordinator Annette Barnie and collaborators (Robert Ehrlich, Denis Daneman, Kusiel Perlman, and Larry Leiter), the University of Toronto Centre recruited and implemented intensive diabetes therapy in adults and children with type 1 diabetes during the feasibility phase of the study. Subsequently, the team successfully enrolled the required patient cohort into the long-term trial. Bernie played a major leadership role in the DCCT and the long-term epidemiologic follow-up study EDIC (Epidemiology of Diabetes Interventions and Complications), chairing various committees and

Bernie proudly displaying his personalized DCCT license plate.

serving as vice chair of the study group. Long-lasting friendships were established with many DCCT/EDIC colleagues, including David Nathan, Oscar Crofford, Saul Genuth, and John Lachin, to name a few.

The DCCT recruited 1,441 participants with type 1 diabetes randomized to the standard conventional therapy of the time or the more experimental intensive therapy. Given the dramatic benefit demonstrated by the intensive therapy arm, the study was stopped early after a mean follow-up of 6.5 years. In 1993, at the American Diabetes Association meeting in Las Vegas, the DCCT Research Group shared the results with thousands of health care attendees in a packed convention hall. You could hear a pin drop as the final results were presented, ushering in a new era in the management of type 1 diabetes (9). The dramatic benefits of intensive therapy in preventing and reducing the progression of retinopathy, nephropathy, and neuropathy were groundbreaking and established intensive therapy (multiple daily insulin injections or insulin pumps with frequent blood glucose monitoring) as the standard of care for the management of type 1 diabetes. One metric of this landmark study's impact is reflected by the now classic status of the DCCT *New England Journal of Medicine* article (9), still the most highly cited diabetes research publication.

The DCCT/EDIC study is approaching 40 years of follow-up and represents the most comprehensively evaluated longitudinal cohort of people with type 1 diabetes. The study continues to contribute new knowledge surrounding the microvascular, macrovascular, metabolic, genetic, quality-of-life, and long-term consequences of type 1 diabetes (10–14).

In 1993 Stewart Harris, the medical director for the Sioux Lookout Zone, approached Bernie to develop a collaboration evaluating the impact of diabetes on the First Nation Community of Sandy Lake, located in northwestern Ontario. With a start-up grant from the NIH and subsequent funding from Canadian agencies, the Sandy Lake Health and Diabetes Program was crafted, with Anthony Hanley as the initial research coordinator. He later became principal investigator of the Sandy Lake Health and Diabetes Program and full professor in the Department of Nutrition Sciences at the University of Toronto. Regular trips to Sandy Lake on Bearskin Airlines via Thunder Bay and Sioux Lookout provided a unique opportunity to experience the realities of health care delivery to a remote indigenous population. With community collaboration, the high rates of diabetes, associated metabolic abnormalities, and devastating complications were carefully documented (15–20). These observations resulted in the initiation of community-based, culturally appropriate intervention programs.

The notion of preventing diabetes and its progression became popular, and various studies utilizing lifestyle interventions, metformin, or thiazolidinediones were initiated. Bernie decided to evaluate this concept, utilizing a novel approach with low-dose combination therapy to improve efficacy of the intervention while reducing adverse effects of the medication. Indeed, the CANOE (Canadian Normoglycemia Outcomes Evaluation) study first demonstrated that progression from prediabetes could be reduced with low-dose metformin and rosiglitazone therapy without the commonly associated adverse effects of these agents seen when they were used at their typical therapeutic doses (21,22). This led to Bernie being one of the first proponents of combination therapy initiated early in the course of diabetes, often using lower yet effective doses of medicines to improve tolerability, a concept that is slowly becoming more accepted (23).

It has been well recognized that the progressive nature of type 2 diabetes is primarily a consequence of β-cell failure. In collaboration with Ravi Retnakaran, at the time a rising star and protégé and who is now full professor at the University of Toronto, a series of innovative studies were initiated to determine if early type 2 diabetes can be put into remission. Ravi documented the impact of early intensive insulin therapy on β-cell

Jean and Bernie Zinman on the occasion of Bernie receiving the Order of Canada from the Governor General, Queen Elizabeth's representative in Canada.

Bernie Zinman establishing the Leadership Sinai Centre for Diabetes at Mt. Sinai Hospital.

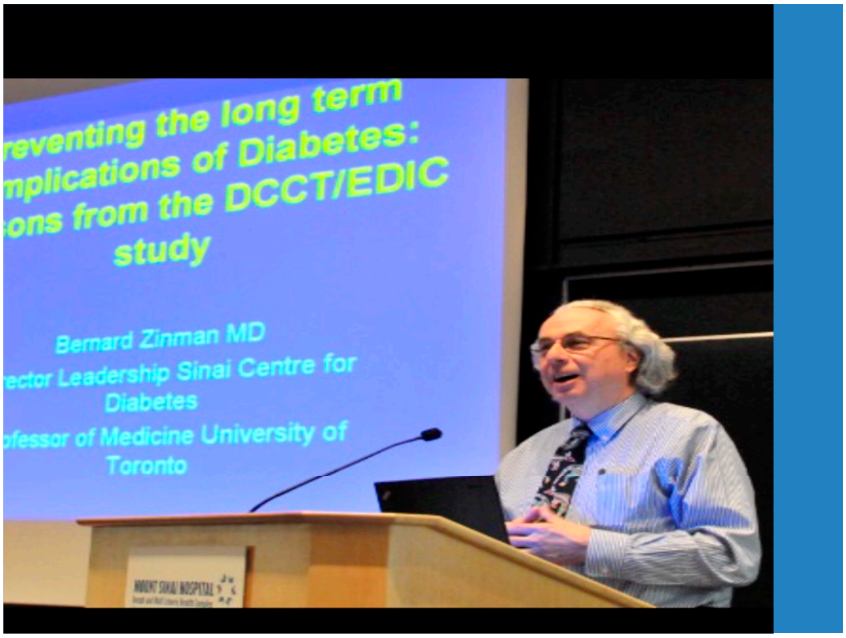
function and evaluated other diabetes treatments in a similar fashion (24–26). In addition to Ravi, Bernie has mentored numerous trainees and junior faculty, including Bruce Perkins, Caroline Kramer, Louis Maple Brown, Stewart Harris, Alice Cheng, Hertzel Gerstein, Elaine Tsui, and Sergio Zuniga, to name a few. In this context, he was awarded the first University of Toronto Department of Medicine Mentorship Award in 2007.

Beyond traditional metrics encompassing improving glycemic control, Bernie was an early proponent of evaluating composite outcomes that included the extent of weight reduction and decreased hypoglycemic risk (27). However, the concept that a diabetes therapy can truly have added value independent of its glucose-lowering properties was first realized when Bernie and his collaborators presented the results of EMPA-REG OUTCOME (BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) in 2015 at the European Association for the Study of Diabetes in Stockholm, with its simultaneous publication in the *New England Journal of Medicine* (28,29). This trial was initiated because of the U.S. Food and Drug Administration requirement to demonstrate acceptable safety of new diabetes therapies. Given Bernie's clinical investigator experience, Boehringer Ingelheim asked him to chair an academic/industry steering committee to lead and then implement and report the results of EMPA-REG OUTCOME. This trial demonstrated, for the first time, that a diabetes therapy developed to lower glucose also reduced cardiovascular mortality by 38%, hospitalization for heart failure by 35%, and all-cause mortality by 32% while simultaneously reducing the progression of renal disease (30). This seminal trial and the related studies that soon followed ushered in a major shift in the paradigm of type 2 diabetes therapy. Indeed, the findings were soon replicated, confirming and extending the EMPA-REG OUTCOME results. Sodium–glucose cotransporter 2 inhibitors, initially utilized by endocrinologists, soon became cardiovascular and renal therapies enthusiastically adopted by cardiologists and nephrologists.

Bernie has also played a leading role in many other important studies, including ADOPT (A Diabetes Outcome Progression Trial), HOPE (Heart Outcome Prevention Evaluation), RASS (Renin Angiotensin System Study), DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), and DEVOTE (Insulin Degludec versus Insulin Glargine in Subjects with Type 2 Diabetes at High Risk of Cardiovascular Events), to name a few. In LEADER it was particularly rewarding to see a second class of diabetes therapies, the glucagon-like peptide 1 receptor agonists, exhibit a beneficial effect on cardiovascular complications, reducing weight and HbA_{1c} without an increase in hypoglycemia (31). Given his sustained contributions to diabetes care and research, the Canadian government awarded Bernie membership in the Order of Canada. In 2019 Bernie was promoted to Officer in the Order of Canada.

Academic leadership has always been an important component of Bernie's interests, and in 1991 he became head of the newly combined Division of Endocrinology at Mount Sinai Hospital and University Health Network. This was the first combined division within medicine at the two hospitals and was not without controversy, for the usual territorial reasons and somewhat different cultures at the different institutions. Bernie successfully unified three groups of endocrinologists at Mt. Sinai Hospital, the Toronto Western Hospital, and the Toronto General Hospital, paving the way for all subspecialty divisions at these institutions to be combined under a single leadership. In 1993 he took on the responsibility of Director of the Banting and Best Diabetes Centre at the University of Toronto, following in the footsteps of Charles Hollenberg. Subsequently, in 2000 he established the Leadership Sinai Centre for Diabetes at Mount Sinai Hospital and held the inaugural Pencer Family Chair in Diabetes. This center quickly grew with the recruitment of new faculty and a comprehensive talented research and clinical health care team, becoming one of Canada's leading diabetes programs.

Bernie has shared his work globally and at home through hundreds of publications and presentations. His knowledge of diabetes and leadership in major clinical trials made him a sought-after speaker. Despite his enthusiasm for his professional career, family has always been the number one priority for Bernie and Jean. Their greatest joy is to have family celebrations that include their three children and four grandchildren. Their cottage on Lake Simcoe is a beehive of activity, particularly in the summer and fall months, with children, grandchildren, and their friends swimming, boating, or walking around the "point." On a daily basis, you can see Bernie with his helmet and red shirt



Bernie Zinman presenting the DCCT results at Medical Grand Rounds in Toronto.

(Jean's insistence for safety reasons) biking the old rail trail and country roads. Having long tried to emulate Bernie's professional achievements, I found myself admiring his success in attracting his extended family to the cottage each weekend. Enlisting Jean's help, we soon found ourselves a neighbor of Jean and Bernie at the lake, with a cottage on the same road a few hundred yards away. Although my office has been on the same floor as Bernie's at Mt. Sinai Hospital for 15 years, some of our most memorable conversations have taken place by the lake, with our flair for recounting stories occasionally embellished by a mutual beverage or two.

In profiling Bernie Zinman, it is indeed remarkable that, in striving for his overarching goal of improving the care of people with diabetes through clinical investigation, he was able to successfully participate on the frontlines as a leader of research advances that have changed the management of both type 1 and type 2 diabetes, as now universally reflected in current guidelines. We recently celebrated the 100th anniversary of the discovery of insulin in Toronto, and we were pleased to have Bernie give the opening lecture describing that transformative discovery. Canada can be proud that progress in diabetes research, clinical care, and health care innovation continues to advance strongly through the efforts of many Canadian scientists mentored by Bernie, who look up to and strive to emulate the sustained excellence that Bernie has achieved over several decades. In closing, Bernie has made a substantial positive difference in many lives and has managed to carry himself with distinction, leading diabetes trials and seeing people with diabetes in the clinic while befriending the majority of people he interacts with. A class act in everything he does, Bernie deserves our thanks for reminding us that one can be a highly respected mensch, without sacrificing excellence. I look forward to continuing to learn from Bernie as he moves on to the next chapters of an already illustrious, distinguished career.

The extended Zinman family. Front row, left to right: Judah Cooper, Robbie Cooper, Julia Zinman, Bernie Zinman, Jean Zinman, Sage Cooper, Lorne Zinman, and Abby Zinman. Back row, left to right: Debbie Zinman, Andrew Zinman, Nikki Zinman, and Bev Young.

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