Dr. Mladen Vranic—A Legend in Diabetes Research: 1930–2019

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Mladen Vranic, MD, DSc, FRSC, FRCP(C), FCAHS, was an early pioneer in the field of diabetes, greatly advancing our understanding of diabetes physiology. Over the course of his scientific career, Dr. Vranic changed the landscape of diabetes research in North America and internationally through his groundbreaking work in glucose metabolism, exercise, stress, and hypoglycemia. It is noteworthy that he trained as the last postdoctoral fellow of Dr. Charles Best, a codiscoverer of insulin, at the University of Toronto.

Dr. Vranic's interest in diabetes research started during his early life, as did his determination to thrive despite deep struggles. He was born 30 April 1930 to Vladamir and Ana Vranic in Zagreb, Croatia. His father was a professor at the Faculty of Economics, Engineering, and Sciences and dean at the School of Economics and Engineering at the University of Zagreb. His teaching specialty was mathematics. Mladen was an only child, of Jewish heritage, and a Holocaust survivor. He and his family narrowly escaped capture by the Nazis multiple times during World War II. As a young boy he, his parents, and his grandmother sought refuge in Italy, managing to flee just ahead of their would-be captors. Despite their efforts, they were eventually caught and sent to a concentration camp when Mladen was 11. He attributed his survival there to his and his family's undeterred tenacity to endure and escape.

Mladen Vranic

Upon completing medical school at the University of Zagreb, Mladen pursued graduate studies in physiology, with a focus on diabetes, the only specialty available in the department at the time. Concomitantly, his father developed type 2 diabetes. Mladen said about the field that was to become his life's work and passion, "I have never regretted for one instant my commitment to a life in medical research and education" and "diabetes offers an incredible number of possibilities in research" and "stimulated my curiosity."

His next move was to change the course of his life and career. After completing his PhD thesis in 1962, he contacted Charles H. Best, codiscoverer of insulin along with Frederick Banting 40 years prior, to explore the possibility of continuing his work in Toronto. Charles Best was head of the University of Toronto's Banting and Best Department of Medical Research at the time. Mladen had just published an article in *Diabetes* that examined the hypothesis that pancreatic β-cells can arise from the ducts of the exocrine pancreas (1). Charles Best's interest in Mladen's article led to an invitation to give a seminar at the University of Toronto. He was then recruited to Toronto and became the last postdoctoral fellow of Dr. Best, who Mladen said "always had time for people" and "was extremely enthusiastic and supportive." Interacting with local and visiting research experts while working at the Best Institute increased Mladen's exposure to work on the pathogenesis of diabetes, its complications, and possibilities for treatment. This was the start of a 60-year distinguished career in diabetes research and education at the University of Toronto, including as Professor (1972–2019) and Chair of Physiology (1991–1995) and Professor of Medicine (1978–2019). It is noteworthy that during a sabbatical leave he was a visiting

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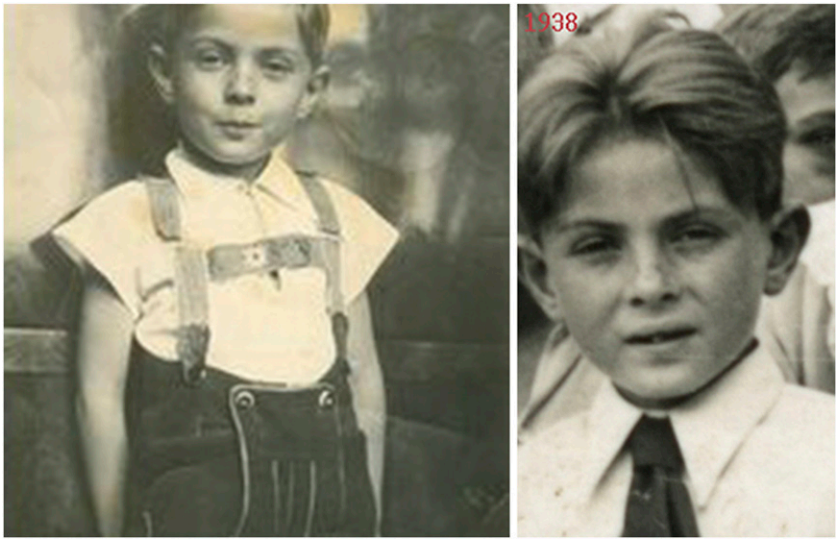


Left panel: young Mladen; right panel: 8-year-old Mladen

research fellow at Merton College within Oxford University (1976–1977).

Mladen's seminal work in diabetes at the University of Toronto resulted in the publication of 214 peer-reviewed journal articles and 70 book chapters. His research reflects both the work of his own graduate students and postdoctoral fellows (over 50 in total) and a wide array of collaborators in both basic science and clinical investigation. His first major contribution was to implement the use of new tracer methods in physiological studies that enabled accurate measurement of steady- and nonsteady-state glucose turnover for the first time (2, 3). This work opened the field to identification of the effects of hormonal and metabolic perturbations on glucose metabolism in both the normal and diabetic state, including some of the first clinical tracer studies relating to insulin resistance, hypertriglyceridemia, and the Cori cycle in humans. In the latter half of his career, he fine-tuned our understanding of defects in glucose and insulin metabolism in diabetes at the cellular and molecular levels, demonstrating impairments in GLUT2 expression during acute hyperglycemia and, along with others, separating the direct and indirect effects of insulin on the liver (4).

Another early important finding was Mladen's discovery of extrapancreatic glucagon (5,6), which changed the prevailing dogma at the time that any given hormone is only produced in one specific gland. His early studies of glucagon action on glucose production provided important support for Roger Unger's idea that glucagon played a key physiological role and that its dysregulation contributed to the diabetic phenotype.

Mladen further established new concepts regarding the role of exercise in diabetes, identifying physiological and molecular mechanisms whereby exercise ameliorates or prevents the onset of type 2 diabetes (7–12). Through his work, he founded the first international symposium on exercise and diabetes, which still has a major impact today. As an additional consequence, his work in the exercise field led to precise methods of controlling insulin administration during exercise in the individual with diabetes, thereby enabling athletes with type 1 diabetes to participate at the highest level in various sports.

Mladen also went on to open up a new field in the area of stress and diabetes. He delineated the physiological and molecular mechanisms responsible for increased stimulation of the hypothalamic-pituitary-adrenal (HPA) axis in type 2 diabetes and how it leads to defects in glucose turnover and hyperglycemia, as well as interventions that effectively ameliorate it (13–16). In opposition to the deleterious effects of chronic stress, he strikingly showed that intermittent neurogenic stress prevents the onset of type 2 diabetes, similar to exercise (17–19). Paradoxically, in his later years, he identified the molecular mechanisms responsible for the diminished response of the HPA axis, catecholamines, cortisol, and glucagon to insulin-induced hypoglycemia in diabetes (20–21). He then introduced a novel approach to ameliorate hypoglycemia in diabetes by blocking the effect of pancreatic somatostatin on the pancreatic α-cell and thereby increasing glucagon secretion (22–23). Mladen summarized his key research accomplishments in a career retrospective published in the *American Journal of Physiology–Endocrinology and Metabolism* (24).

Dr. Vranic's exceptional scientific body of work was recognized in 1991 by the foremost international diabetes research award, the American Diabetes Association's Banting Medal for Scientific Achievement. As an acknowledgment of his research excellence in diabetes translational medicine, he is also the recipient of a multitude of other leading awards and honors; a selected list includes the American Diabetes Association's Albert Renold Award for a distinguished career in the training of diabetes research scientists and facilitation of research (2005), the Solomon A. Berson Distinguished Lectureship of the American Physiological Society Endocrinology and Metabolism Section (1995), the Canadian Diabetes Association Inaugural Lifetime Achievement Award (2007), Laureate of the Canadian Medical Hall of Fame (2009), and Officer of the Order of Canada (2010). Dr. Vranic is additionally the recipient of 18 honorary degrees, including ones from Karolinska University and the University of Toronto.

Mladen's First Graduate Student

By Alan Cherrington

I was Mladen's first graduate student and began work in his laboratory in 1968. I decided to go to graduate school after working in a research laboratory at the Food and Drug Directorate in Ottawa. In fact, I was fascinated by physiology and could have worked in any area of the discipline, but as fate would have it Mladen had just been appointed to the faculty at the University of Toronto and he was looking for a graduate student. I knew very little about diabetes, but that quickly changed. I was involved in Mladen's early studies of glucagon action and the discovery of nonpancreatic glucagon. Mladen was a terrific mentor, not only teaching me the meaning of first-rate science but also showing me how to balance research and family life. He was indeed a wonderful spouse and parent, something I try to emulate and instill in my own trainees. Mladen

Mladen Vranic and Alan Cherrington upon Alan's Outstanding Research as a Young Investigator Award from ADA

supported me in many ways through my career and I continued to visit him even as his health declined. I was by chance in Toronto when Mladen passed and had the honor of being a pallbearer at his funeral. Two things were most striking to me on that occasion: first, the number of people whose lives he had touched and who were present for the celebration of his life; second, the warmth with which his daughters and his wife, Linda, spoke of him. His was truly a life well lived.

An Introduction to Quality Scientific Research

By Shirya Rashid

I first met Mladen when he was Chair of the Department of Physiology at the University of Toronto in the 1990s. My introduction to scientific research excellence was through Mladen, as it was for countless other scientists and leaders in diabetes that had the good fortune to be mentored by him. Mladen considered the success and impact of (his) students and fellows to represent the most important achievement of (his) scientific career.

My first encounter with Mladen was in an interview for a graduate studentship in his laboratory. I had been carrying out a research stint at Penn State University in the Department of Exercise Physiology and wished to return to Canada to pursue a master's degree in physiology. I knew that the University of Toronto's Department of Physiology was the leading program in Canada and wished to apply to Mladen, who was Chair of the department. If I didn't know his legendary status at the time, I soon became aware of it. Mladen's call to me at Penn State was routed through the office of Penn State's Chair of Exercise Physiology (my supervisor) at that time. He later explained that Mladen was one of the foremost pioneers in the study of exercise physiology in diabetes, among a multitude of other areas of research excellence in diabetes. Needless to say, my interview with Mladen went well. He gave me a publication of his on the impact of stress on the development of hyperglycemia in diabetes, which had a strong impact on me. It became my research focus in his laboratory and led to my initial first-authored article on the amelioration of hyperglycemia from stress in diabetes through hyperinsulinemia and β-blockade, published in *Diabetes* (16) and highlighted by Reuters news agency as a major find in 2000.

Through the years, our relationship grew from mentor-mentee to collaborator-colleague and then friends. Mladen had many wonderful personal attributes. As a mentor and adviser, he was always patient and personable, teaching by hand with ruler and pencil in tow the importance of reading and interpreting raw experimental data and graphs. Given his prolific scientific writings, he always had an instructional journal article, text chapter, or book of his, his mentees, and collaborators in hand from the full shelves of his office. He was even-tempered and remained calm in the midst of conflicts and crises and was optimistic about the outcomes. He recommended the same for his trainees, valuable advice when experiments inevitably initially failed and grant and manuscript deadlines were in near sight.

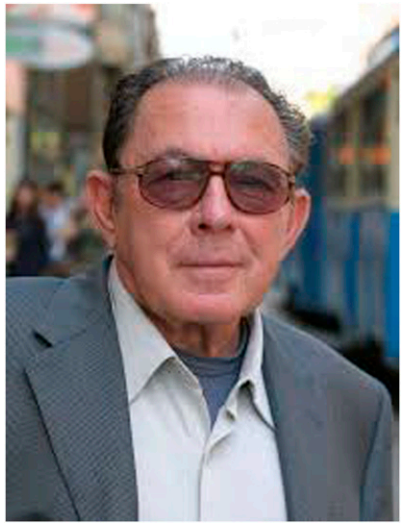
Very apparent was his curiosity for all things scientific and, in this respect, he was an inventive thinker. At honorary speeches, he would often quote Robert Frost's "The Road Not Taken" as the route to originality, which he felt was a key to his success and to success in the arts and science:

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

His curiosity also extended to a love of classical music, literature, theater, and cultures. His speeches over the years are liberally filled with quotes from global works of great literature. Indeed, the title of his autobiography is taken from Greek mythology: "Odyssey Between Scylla and Charybdis. . .: A Career Retrospective" (24). He had a genuine interest in the background and cultures of his very diverse research groups over the years, something that was reflected in his varied collection of heirloom books of ancient cultures. Consistent with this interest, he learned to speak six languages—English, Italian, French, Russian, Croatian, and German—and did quite well in Latin, also.

Mladen would probably also say not to "just take the road not taken" but to just take the road and move forward with determination according to his own motto: "I don't give up easily. In fact, I never give up at all." This maxim applied to his tenacious approach to probing for answers in science and to his life, a life well lived but not without struggle. Many of his scientific breakthroughs came after his recovery from a stroke in later life, including acquiring a patent during his final years on a putative new method for alleviating hypoglycemia in diabetes, one of the most frequent and serious acute complications of insulin-treated diabetes. The new approach involved blocking the effect of somatostatin to lower the potential of hypoglycemia. This discovery later went into drug development with start-up Zucara Therapeutics in conjunction with MaRS, University of Toronto, and the Centre for Drug Research and Development (CDRD).

Despite such challenges in life, Mladen was well known for a personality that



Mladen during a visit to Zagreb, Croatia, where he received an award from the Croatian Academy of Medical Sciences

exhibited great humor, wit, and charm and a great deal of generosity. He not only trained multiple generations of diabetes scientists and leaders but also supported them throughout their careers. In terms of myself, he advised me throughout my career in translational metabolism and cardiology research, provided me with ready letters of support and recommendations, and accepted featured lectures at my university during my professorships. While it was usually Mladen who generously nominated investigators for awards, I was honored to have cosponsored an honorary doctorate for him granted by McMaster University (2013) during my tenure there.

Mladen died of congestive heart failure 18 June 2019 at the age of 89. He leaves behind his wife Linda Vranic, director at Magnus Associates, with whom he has two daughters, Claire Vranic, a director at the Canadian Imperial Bank of Commerce, and Anne Vranic, a communications specialist at the Royal Ontario Museum. His daughter Iva Vranic, from his first marriage to his late wife Magda Vranic (who herself was an Assistant Professor of Rehabilitation Medicine at the University of Toronto), is a securities lawyer and director with the Bank of Nova Scotia.

For many of us, his exceptional work and wonderfully larger-than-life personality will continue to inspire us as the years go by.

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References

1. Vranic M. The effects of cortisol in guinea pigs with normal and atrophic exocrine pancreas. Diabetes 1965;14:194–200
2. Norwich KH, Radziuk J, Lau D, Vranic M. Experimental validation of nonsteady rate measurements using a tracer infusion method and inulin as tracer and tracee. Can J Physiol Pharmacol 1974;52:508–521
3. Vranic M, Wrenshall GA. Matched rates of insulin infusion and secretion and concurrent tracer-determined rates of glucose appearance and disappearance in fasting dogs. Can J Physiol Pharmacol 1968;46:383–390
4. Mathoo JM, Shi ZQ, Klip A, Vranic M. Opposite effects of acute hypoglycemia and acute hyperglycemia on glucose transport and glucose transporters in perfused rat skeletal muscle. Diabetes 1999;48:1281–1288
5. Vranic M, Engerman R, Doi K, Morita S, Yip CC. Extrapancreatic glucagon in the dog. Metabolism 1976;25(Suppl. 1):1469–1473
6. Ross G, Lickley L, Vranic M. Extrapancreatic glucagon in control of glucose turnover in depancreatized dogs. Am J Physiol 1978;234:E213–E219
7. Zinman B, Vranic M, Albisser AM, Leibel BS, Marliss ED. The role of insulin in the metabolic response to exercise in diabetic man. Diabetes 1979;28(Suppl. 1):76–81
8. Minuk HL, Hanna AK, Marliss EB, Vranic M, Zinman B. Metabolic response to moderate exercise in obese man during prolonged fasting. Am J Physiol 1980;238:E322–E329
9. Vranic M, Berger M. Exercise and diabetes mellitus. Diabetes 1979;28:147–163
10. Minuk HL, Vranic M, Marliss EB, Hanna AK, Albisser AM, Zinman B. Glucoregulatory and metabolic response to exercise in obese non-insulin-dependent diabetes. Am J Physiol 1981; 240:E458–E464
11. Douen AG, Ramlal T, Rastogi S, et al. Exercise induces recruitment of the "insulin-responsive glucose transporter." Evidence for distinct intracellular insulin- and exercise-recruitable transporter pools in skeletal muscle. J Biol Chem 1990;265:13427–13430
12. Király MA, Campbell J, Park E, et al. Exercise maintains euglycemia in association with decreased activation of c-Jun NH2-terminal kinase and serine phosphorylation of IRS-1 in the liver of ZDF rats. Am J Physiol Endocrinol Metab 2010; 298:E671–E682
13. Miles PD, Yamatani K, Lickley HL, Vranic M. Mechanism of glucoregulatory responses to stress and their deficiency in diabetes. Proc Natl Acad Sci USA 1991;88:1296–1300
14. Miles PD, Yamatani K, Brown MR, Lickley HL, Vranic M. Intracerebroventricular administration of somatostatin octapeptide counteracts the hormonal and metabolic responses to stress in normal and diabetic dogs. Metabolism 1994; 43:1134–1143
15. Lekas MC, Fisher SJ, El-Bahrani B, van Delangeryt M, Vranic M, Shi ZQ. Glucose uptake during centrally induced stress is insulin independent and enhanced by adrenergic blockade. J Appl Physiol (1985) 1999;87:722–731
16. Rashid S, Shi ZQ, Niwa M, et al. Beta-blockade, but not normoglycemia or hyperinsulinemia, markedly diminishes stress-induced hyperglycemia in diabetic dogs. Diabetes 2000;49:253–262
17. Bates HE, Kiraly MA, Yue JT, et al. Recurrent intermittent restraint delays fed and fasting hyperglycemia and improves glucose return to baseline levels during glucose tolerance tests in the Zucker diabetic fatty rat—role of food intake and corticosterone. Metabolism 2007;56:1065–1075
18. Bates HE, Sirek AS, Kiràly MA, et al. Adaptation to mild, intermittent stress delays development of hyperglycemia in the Zucker diabetic Fatty rat independent of food intake: role of habituation of the hypothalamic-pituitary-adrenal axis. Endocrinology 2008;149:2990–3001
19. Bates HE, Sirek A, Kiraly MA, et al. Adaptation to intermittent stress promotes maintenance of beta-cell compensation: comparison with food restriction. Am J Physiol Endocrinol Metab 2008; 295:E947–E958
20. Chan O, Chan S, Inouye K, Shum K, Matthews SG, Vranic M. Diabetes impairs hypothalamo-pituitary-adrenal (HPA) responses to hypoglycemia, and insulin treatment normalizes HPA but not epinephrine responses. Diabetes 2002;51: 1681–1689
21. Inouye K, Chan O, Riddell MC, Akirav E, Matthews SG, Vranic M. Mechanisms of impaired hypothalamic-pituitary-adrenal (HPA) function in diabetes: reduced counterregulatory responsiveness to hypoglycaemia. Diabetes Nutr Metab 2002;15:348–355; discussion 355–356, 362
22. Yue JT, Burdett E, Coy DH, Giacca A, Efendic S, Vranic M. Somatostatin receptor type 2 antagonism improves glucagon and corticosterone counterregulatory responses to hypoglycemia in streptozotocin-induced diabetic rats. Diabetes 2012;61:197–207
23. Yue JT, Riddell MC, Burdett E, Coy DH, Efendic S, Vranic M. Amelioration of hypoglycemia via somatostatin receptor type 2 antagonism in recurrently hypoglycemic diabetic rats. Diabetes 2013;62:2215–2222
24. Vranic M. Odyssey between Scylla and Charybdis through storms of carbohydrate metabolism and diabetes: a career retrospective. Am J Physiol Endocrinol Metab 2010;299:E849–E867