PROFILES IN PROGRESS

A Tribute to Robert Roy Henry—The Classic "Academic Triple Threat": Accomplished Researcher, Inspiring Teacher, and Compassionate Clinician

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Robert (Bob) Roy Henry was born 12 March 1950 in Winnipeg, Manitoba, Canada, to Ken and Paula (née Baldwin) Henry. His father was a train engineer and his mother a homemaker from Kent, England. Bob was raised in Transcon, a small town outside the city where most people joined the railway to make a living, and that is what his future looked like also. Bob and his wife, Denine McBeth, first met as teenagers. She was 16 and a cheerleader from a rival high school; he was 17 and owned a motorcycle.

The year following high school graduation he was able to find work at Manitoba Steel as a laborer. It was this experience that convinced him to pursue his education at the University of Winnipeg. Bob had a natural thirst for knowledge and thrived in the academic environment. During the course of his studies, he was in line for an academic excellence award (Canada's recognition of students with outstanding achievements). However, Bob knew it would require another year at the University of Winnipeg and his interests had changed. He decided against pursuing the academic distinction and instead applied to and was accepted at the University of Manitoba in the field of medicine in 1971, graduating in 1975.

In 1973 he and Denine were married, and 2 years later their first son, Ryan, was born. During that time he was the president of the interns and residents' association of Manitoba. After he graduated, he thought seriously of pursuing a specialty in cardiology at the University of Manitoba Health Science Centre. Unfortunately, on 11 September 1976, Bob, Denine, and Ryan were involved in a serious car accident that left Bob deaf from antibiotic-induced ototoxicity and with severe orthopedic limitations that would require numerous surgeries and rehabilitation. Months later, while still in rehabilitation and not knowing what the future held, he received a visit from Dr. Chuck Fainman, the head of endocrinology at the Health Sciences Centre, who offered Bob a position in endocrinology. Thus began Bob's journey in the field of diabetes, as well as a lifelong friendship with Chuck.

Robert R. Henry, MD

Bob Henry: The Early Years

By Jerrold Olefsky

Bob Henry and I have been long-time friends and colleagues since 1982. At that time Bob was already an Assistant Professor of Endocrinology at the University of Manitoba in Winnipeg. He sent me a letter (these were pre-email days) expressing an interest in further clinical research and further training in metabolic diseases. By that time, I had been at the University of Colorado in Denver for 4 years and felt that the program was sufficiently well established to accommodate additional scientists. He, his wife Denine, and family were happy to move to Denver to thaw out from the Winnipeg winters, enjoy the sunshine, and dive into clinical research! Bob had a strong passion for diabetes-related clinical research, and after arriving in Denver he never looked back. He quickly learned all the tools of the trade, including hyperinsulinemic-euglycemic clamps, tracer

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Left panel: Bob at 4 years old; right panel: Bob at graduation from the University of Manitoba, 1975

methodologies, and adipose tissue biopsies, and rather quickly became a productive investigator. The following year we all relocated from Denver to the University of California, San Diego (UCSD), and Bob gladly made the move, looking forward to more sunshine, warmer weather, and more metabolic research.

Bob has always been completely focused on translational research to help explain the causes of and develop new treatments for diabetes. Once in San Diego, he set up shop at the Veterans Affairs (VA) Hospital and plunged back into his work. His focus was on mechanistic-based clinical research, the use of human cells or biopsies ex vivo, and the rapidly expanding field of diabetes-related clinical trials. Using tracer studies, combined with indirect calorimetry, several of his projects showed that glycogen synthesis was defective in insulin-resistant states. He carried out a number of studies on this topic, exploring differences in glucose storage (i.e., glycogen production) and glucose oxidation in a variety of metabolic conditions. This sparked his interest in more mechanistic studies, and he developed a focus on glycogen synthase kinase 3 (GSK-3) as a component of the defects in glycogen synthesis he observed in his in vivo studies. His subsequent studies on this topic were key to the field, putting GSK-3 on the map as a component of insulin resistance and opening a new area for drug discovery.

One of Bob's initial interests centered on obesity. Early on, he recognized the prevalence of obesity and what an enormous toll it took on patients with type 2 diabetes (T2D). He performed seminal clinical studies defining the effects of weight loss to reduce glycemia, lower plasma insulin levels, and improve insulin sensitivity. He also found that when patients who had lost weight regained it, as so many of them do, they ended up back in the same metabolic situation they were in before weight loss started.

At this point, he developed a strong interest in bringing his in vivo studies to the laboratory bench, but he wanted to keep his work focused on human disease. To accomplish this, he developed a system to culture human skeletal muscle cells from muscle biopsies and, together with his colleague Theodore Ciaraldi, he was able exploit this new methodology to develop new concepts related to skeletal muscle insulin action and physiology. For example, he was able to elucidate the defects in muscle glycogen metabolism in this system, which closely recapitulated his in vivo findings on glucose storage in obesity and T2D.

Bob's work has clearly been instrumental in furthering our understanding of the basic pathophysiology of T2D, obesity, and insulin resistance. Beyond these basic contributions to the science of metabolic disease, Bob's studies have also had major and direct impact on our approaches to treatment of patients with T2D. Through his clinical trial studies, he has helped in the development of new drugs, which are now in the clinic or in late-stage clinical development. In this way, his efforts have added to our therapeutic armamentarium providing multiple new options for anti-diabetes treatment.

Bob Henry: My Friend

By Alain Baron

I first met Bob in 1982 when we were endocrinology fellows in Jerry Olefsky's laboratory at the University of Colorado. Our careers and relationship have tracked in ways we could not have anticipated. We eventually joined the UCSD faculty at the same time and for 3 years shared an office on the 3rd floor of the San Diego VA Hospital, the same one he occupied until retirement. Our families have been close friends. I wish we could spend more time together, as the times we did have were very meaningful. While Bob's career is remarkable for its excellence and prodigiousness, Bob's greatest impact has been on the people who have had the joy to get to know him and observe him as a role model as I did. It is hard to describe, but on occasions when I talk to Bob about career and family, I have a sense that he is teaching me what is important in life and how to extract the most out of the moment. Bob is grateful every single day for his family, friends, career, and the mere simple pleasure of driving the San Diego coast highway to work. "Carpe diem" could not suit anyone better.

Bob's sense of humor, often self-deprecating, made him a delight to be with. Bob's optimism, enthusiasm, and grace also belies a strong realist within. Those who work with him know and admire his high standards, integrity, fairness, and decisiveness. He is passionate about his work but never more so than for his family. Denine, Ryan, Danny, Dustin, Bob's grandchildren, and his daughters-in-law are his life's center, his renewable source of pleasure. I will never forget watching Bob and Denine dancing with abandon at Steve Edelman's wedding. They are an inseparable pair, close even at professional meetings, drawing strength and comfort from each other. What a great example for all to see, but one only few could emulate. Bob and Denine have shown us how to live a full and rewarding life and for that we are in their debt.

Top panel: Bob and Denine's wedding day, 1973; bottom panel: Bob and Denine in recent years

Bob Henry—The Classic "Academic Triple Threat"

By Sunder Mudaliar and Ted Ciaraldi

Bob Henry embodies the classic definition of an academic triple threat. Whether it is clinical research, patient care, or teaching medical students, residents, or fellows, Bob always gives it his very best. When I (Sunder Mudaliar) first met him in early 1994, Bob Henry advised me that to be a complete physician, one should excel not only in clinical practice but also in teaching and clinical research. I took this advice to heart.

Under Bob's hands-on guidance, many fellows and faculty were trained on the hyperinsulinemic-euglycemic clamp. He also introduced the concept of indirect calorimetry to many trainees, along with all the raw calculations needed to measure carbohydrate/fat and protein oxidation. This was done not using a commercially available device but rather a machine that was built by Bob himself from scratch using sophisticated O_2 and CO_2 monitors and other components bought from Home Depot!

The mid- to late-1990s saw an explosion of new therapies approved for the treatment of T2D. From being limited to the use of sulfonylureas and long- or short-acting insulins, the field of diabetes therapeutics greatly expanded with the introduction of metformin, the thiazolidinediones, the incretins, the sodium–glucose cotransporter 2 (SGLT2) inhibitors, and all the long/short/rapid analog insulins. Bob was instrumental in performing and guiding trials studying all drug classes. Bob performed some of the early human studies with troglitazone and other glitazones, insulin analogs, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 agonists, and finally the SGLT2 inhibitors. He was often principal investigator of these trials and made sure their designs addressed important mechanistic insights and clinical outcomes. For example, Bob's group proposed a novel hypothesis, positing that the cardiorenal benefits of SGLT2 inhibitors may be due to a shift in fuel metabolism away from fat and glucose oxidation, which are relatively energy inefficient, toward more energy-efficient ketone bodies, thus improving cardiorenal function. Bob also performed one of the first clinical studies demonstrating that tight glycemic control can be obtained using intensive, conventional split-dose insulin therapy in the outpatient management of type 2 diabetes without development of unacceptable side effects. This was one of the studies that led to the development of the split-mix 70/30 insulin combination for patients with T2D. In addition, Bob participated in several multicenter studies including the VA Diabetes Trial (VADT), the National Institutes of Health–sponsored Diabetes Prevention Program (DPP), and the Glycemia Reduction Approaches in Diabetes (GRADE) study.

One of Bob's passions is human skeletal muscle and adipose tissue culture systems. In addition to his clinical research activities above, Bob has been actively involved in bench research and passionate about bridging the gap between the bench and the bedside. Bob's laboratory is among the pioneers in the validation of human skeletal muscle and adipose tissue culture systems. Work in Bob's lab helped reveal the intrinsic and acquired aspects of the metabolic phenotypes of T2D and polycystic ovary syndrome in those tissues. His group has shared their methodologies with investigators from multiple laboratories around the world. His laboratory also employed these systems to investigate the impact of diabetes and obesity on the synthesis and secretion of adiponectin and myokines, the latter being a set of small proteins and proteoglycan peptides that are synthetized, expressed, and released by skeletal myotubes. Studies from Bob's lab were among the first to demonstrate that altered secretion of a number of myokines is an intrinsic property of skeletal muscle in T2D, suggesting a putative role of myokines in the response of skeletal muscle to T2D, including the reduced capillary density of muscle in diabetes.

Bob has also been very involved in several recent novel studies in patients with type 1 diabetes. These included the first in-human stem-cell therapy for type 1 diabetes using ViaCyte's human cell–derived pancreatic progenitor cells, called PEC-01 cells, and mechanistic studies involving glucagon receptor antagonists.

Finally, to cap off Bob's prodigious career, we would be remiss not to mention his foray into entrepreneurship. In 2003, Bob founded Diobex, a start-up focused on diabetes and obesity therapeutics. In this context, Bob was the first to propose the use of low-dose glucagon to prevent insulin-induced nocturnal hypoglycemia in patients with long-term type 1 diabetes. Today, this concept is the scientific basis for many companies developing better approaches to the treatment of type 1 diabetes.

Bob Henry: My Teacher, Role Model, and Friend

By Steve Edelman

I first met Bob Henry at the start of my endocrine fellowship at UCSD in 1987. Over the ensuing 30+ years, I have had the honor and privilege to be friends and work closely with such an incredible individual as Bob.

Bob mentored me closely and helped me navigate the ever-changing political, bureaucratic, and academic maze of a major university. He always maintained an open-door policy to help anyone who sought him out, including undergraduates, medical students, residents, fellows, nursing staff, and other junior and senior faculty members.

Bob is second to none when it comes to role models, in both life in general and work. Teaching others to do the right thing is always first and foremost for him. He is insightful and incredibly generous with his time, demonstrating a great

Top panel: Bob and Denine with their sons, Dustin, Daniel, and Ryan (left to right); middle panel: Bob and Denine with their family in 2011 (left to right, back row: Ryan, Dustin, Daniel; second row: Sarah [Ryan's wife], Bob, Denine, and Tiffany [Daniel's wife]; children: Trevin, Gavin, Taylor, Sean); bottom panel: Bob and Denine's grandchildren (Taylor, Trevin, Brittany, Sean, Gavin)

sense of honesty, integrity, and loyalty with his friends, coworkers, and family. Bob has a unique way to make those around him feel special. He would give the shirt off his back to anyone in need.

Vanita Aroda's comment says it all about Bob. "To know that all of us around the world that have been mentored by Dr. Henry and are able to share forward his legacy through our own day-to-day interactions with others is precious. Dr. Henry role modeled for us both the importance of scientific rigor and selfless dedication in mentorship. He gave us the spirit of being able to educate others, to bring science, research, and medicine to life, and to proceed with curious minds, open hearts, and a respect for the continued learning journey. We appreciate these gifts as Dr. Henry's love and what we hope we can share going forward: mentorship, from the heart."

Bob and Denine display to all that know them the epitome of a true lifelong partnership. They raised three boys to become respectful, hardworking, and polite young men emulating many characteristics of their parents.

Very few people in this world go through life without "burning any bridges" and Bob is one of them. Bob does not hold grudges, a remarkable feat in a long career and testament to his deeply genuine accepting disposition. We all have learned greatly from Bob about how to respond to and deal with adversity and what seems like an unfair imbalance of tragedies that have affected his family. Bob's ever-present natural and innate sense of humor, along with a warm smile and gleam in his eyes, makes others feel comfortable and welcome. This is true during hospital rounds, medical school lectures, and national and international meetings, which makes him an effective and well-liked teacher and educator. The world would be a better place if there were more Bob Henrys.

Bob is 5 years older than myself, and as we aged over the years I would kid him about how old he was on his birthday every year and he would always reply, "Steve, the percent different in our ages is getting smaller," and give me his classic smile. Speaking for all those who know him, we are blessed to have Bob Henry among us. His positive impact will be felt for many years to come.

The Road Taken

The road taken is not always easy, and Bob's deafness and physical limitations proved difficult at times, but they never stopped him. Bob took a sabbatical in Edinburgh, Scotland; was President, Medicine and Science, of the American Diabetes Association (ADA) (2011); and was recently presented with the lifetime achievement award at the ADA's 79th Scientific Sessions (2019). He also served on several boards including the American Association of Clinical Endocrinologists, participated on numerous high-level advisory boards for several companies developing groundbreaking advances in the field of diabetes, and served as an Associate Editor for *Diabetes Care*. Despite pain and physical challenges, a residual effect of the accident decades ago, he enjoyed river rafting, diving the Great Barrier Reef, fishing with his grandchildren, taking long walks on Torrey Pines Beach, and dancing with Denine, the love of his life.

Though his career is important to him, his family means much more. Bob and Denine feel blessed by having raised three boys together, but even that couldn't rival the joy of their five grandchildren. Bob spends as much time as possible with his grandchildren (three boys and two girls), who give him lots of love and laughs and affectionately refer to him as "Buppa." When they come, he never fails to greet them or send them home with a licorice treat. Their time together is taken up with a game of UNO or walks along the cliffs. Bob loves life!

Bob has always been amazed at the development of his life and feels strongly that he was guided toward the path he took. We would add: and for that, the field of diabetes has greatly benefited.

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Editor's Note. Dr. Robert Henry's family reports that he passed away peacefully after a long illness on 1 January 2020. Among his more recent contributions to the ADA and to the diabetes community in general, Dr. Henry served as an Associate Editor of *Diabetes Care*. The editorial team of *Diabetes Care* wishes to express their condolences to the Henry family.