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Obituary

A giant in the fields of endocrinology, metabolism, and diabetes research has passed. Roger H. Unger was born on March 7, 1924, in New York City and died in Dallas, Texas, at the age of 96 on August 22, 2020 (Figure 1). Among his indelible contributions were the development of the first radioimmunoassay for glucagon (1), establishment of the hormone's physiologic and pathophysiologic roles (2–4), contributions to our understanding of the role of ectopic fat storage or “lipotoxicity” in development of obesity-related tissue dysfunction (5), and elucidation of novel roles of leptin in regulation of lipid metabolism and pancreatic islet biology (4, 6). Equally impactful was his exemplary track record as a mentor for more than 50 postdoctoral fellows and students over more than 60 years of operation of his independent research laboratory, many of whom went on to highly successful careers in medicine and science in their own right. We write about Roger as two colleagues who worked side by side with him through different time frames, 1980–2002 (CBN) and 2007–2020 (PES). When we compared notes about Roger over the years, two distinguishing qualities immediately rose to the surface. First, he was one of the most creative thinkers that we have ever known, and second, he was blessed with an irrepressible, almost child-like enthusiasm and joy for discovery and [...]

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A giant in the fields of endocrinology, metabolism, and diabetes research has passed. Roger H. Unger was born on March 7, 1924, in New York City and died in Dallas, Texas, at the age of 96 on August 22, 2020 (Figure 1). Among his indelible contributions were the development of the first radioimmunoassay for glucagon (1), establishment of the hormone's physiologic and pathophysiologic roles (2–4), contributions to our understanding of the role of ectopic fat storage or “lipotoxicity” in development of obesity-related tissue dysfunction (5), and elucidation of novel roles of leptin in regulation of lipid metabolism and pancreatic islet biology (4, 6). Equally impactful was his exemplary track record as a mentor for more than 50 postdoctoral fellows and students over more than 60 years of operation of his independent research laboratory, many of whom went on to highly successful careers in medicine and science in their own right.

We write about Roger as two colleagues who worked side by side with him through different time frames, 1980–2002 (CBN) and 2007–2020 (PES). When we compared notes about Roger over the years, two distinguishing qualities immediately rose to the surface. First, he was one of the most creative thinkers that we have ever known, and second, he was blessed with an irrepressible, almost child-like enthusiasm and joy for discovery and new ideas. When developing a new idea, he would need to discuss it and would often walk into our offices to do so, heedless of anything else that we might be doing. A new idea would often gestate all day and all night, sometimes culminating with an 11:00 PM phone call that would start, not with “Hello,” but rather with a phrase such as, “But what if the levels go down?!!?” This joyful dedication to science and new

ideas was infectious for all of the young faculty, fellows, and students who trained at the University of Texas Southwestern Medical Center's Touchstone Diabetes Center, which was founded by Roger in 1986. We would often find our lab trainees



Figure 1. Roger H. Unger, MD.

in Roger's office, listening in rapt attention as he provided advice about their work and shared his newest ideas. This is an irreplaceable element that we have lost with Roger's passing.

Roger grew up in New York City, the son of a well-known physician/hematologist and his stay-at-home mother. He attended the Horace Mann School in New York until age 15 and then finished his secondary school training at the Taft School in Connecticut before earning his undergraduate degree at Yale and MD at Columbia.

His father's two brothers were also physicians, and Roger was committed to becoming a doctor from an early age. He worked at Bellevue Hospital in New York for a time before entering the Public Health Service in 1951, where he was assigned to direct a diabetes detection drive in Dallas, thereby starting his career in endocrine and diabetes research. During this period, he investigated the newly established University of Texas Southwestern Medical School in Dallas, which was then little more than a collection of Quonset huts. Nevertheless, the remarkable growth and development of the school into one of our nation's leading biomedical research institutions was already foreshadowed by the presence of brilliant minds, such as Donald Seldin and Marvin Siperstein, and Roger took note. He returned to New York for a time to open an office as a practicing physician but then decided to return to Dallas to accept a faculty position at the University of Texas Southwestern and the Dallas VA Medical Center in 1956 in order to try his hand at research. He maintained those appointments for the rest of his illustrious 64-year career, during which he was elected to the US National Academy of Sciences (1986) and the American Academy of Arts and Sciences (1994). His ground-breaking work also led to prestigious prizes and awards, including the two highest awards of the American Diabetes Association, the Lilly Award (1964) and the Banting Medal (1975); the highest award of the Endocrine Society, the Fred Conrad Koch Award (1983); and the Rolf Luft Award from the Karolinska Institute (2014).

At the time that Roger launched his research laboratory in Dallas, glucagon was not yet recognized as insulin's critical counterregulatory partner and was only just beginning to be perceived as a protein product (or possible contaminant) of pancreatic islets. Roger wanted to develop radioimmunoassays (RIAs) for insulin and glucagon and knew that

the laboratory of Solomon Berson was working in this area at the Bronx VA Hospital in New York. In a meeting with Berson, Roger realized that he was well on his way to establishing the insulin RIA, using radio-iodinated insulin and insulin antibodies. The two men agreed that Roger would try to develop an RIA for glucagon in parallel with Berson's work on the insulin assay, even though Berson had already tried and failed to develop the glucagon assay. The Berson lab showed Unger and associates how to radio-iodinate glucagon, and the Unger lab successfully developed glucagon antibodies and reported the glucagon RIA in 1959 (1), ahead of Berson's publication of the insulin RIA in 1960 (7). Illustrating his lifelong and endearing attributes of grace, character, and honesty, Unger was careful to credit the Berson group for the critical radio-iodination procedure, and following Berson's untimely death in 1972, his colleague Rosalind Yalow was awarded the 1975 Nobel Prize for the insulin RIA.

With the glucagon RIA in hand, Roger spent the next two decades defining how glucagon secretion from pancreatic islet α cells is regulated by nutritional and hormonal factors, how this regulation contributes to control of fuel homeostasis in normal physiology, and how dysregulated glucagon secretion contributes to development of diabetes and other disease states. He and his many talented fellows created a seamless web of papers describing preclinical studies in rodents and dogs, coupled with an equally deep set of human studies, in aggregate defining the now classical catabolic effects of glucagon on glucose/glycogen, lipid, and amino acid/protein metabolism and the critical role of the hormone as a counterregulatory agent to the anabolic actions of insulin. Perhaps most importantly, Roger put forth the idea that the glucagon/insulin ratio in blood is a critical determinant of fuel homeostasis and that diabetes is not just simply a disease of insulin deficiency, but one of unopposed glucagon action (referred to as "the bihormonal hypothesis") (3, 4). Buttressed by a large catalogue of primary publications in leading journals, which included extensive studies of a third islet hormone, somatostatin, the evolution of his ideas is also chronicled in a parallel series of reviews and edi-

torials in journals such as the *New England Journal of Medicine*, the *Journal of Clinical Investigation*, and *Diabetes* (2, 3, 8). Particularly revealing, and typical of his style of thinking, is an editorial written at an early stage of the experimental work in 1966 (9). The abstract from that paper is as follows: "A teleologic model, based upon currently available knowledge of the gluco-regulatory hormones, insulin, glucagon, and growth hormone, has been presented in an effort to simplify understanding of their physiologic importance. The approach employed in this conceptual "repackaging" stresses in evolutionary terms the contribution of these hormones to the solution of critical problems of energy storage and supply, which, in their absence, would block phylogenetic progress."

This was Roger's genius — the ability to think about physiology as though he was in charge of designing the system to achieve its biological function. Your faithful authors have witnessed Roger using this approach repeatedly, sometimes leading down blind alleys, but just as often resulting in truly novel insights about how physiological systems are constructed.

In 1986, Roger founded the Touchstone Diabetes Center at the University of Texas Southwestern Medical Center, in collaboration with Daniel Foster and J. Denis McGarry, and began to recruit young scientists with training in molecular biology, heralding a transition away from his deep physiologic studies on insulin/glucagon dynamics. Using techniques such as *in situ* hybridization, immunocytochemistry, and adenovirus-mediated gene manipulation, Roger and his collaborators, including his great friend Lelio Orzi in Geneva, performed a series of studies on the role of the GLUT-2 glucose transporter in regulation of insulin secretion and development of β cell dysfunction and type 2 diabetes in rodent models (10). Influenced by a seminal paper about the underappreciated role of hyperlipidemia in pathogenesis of type 2 diabetes by his friend and colleague J. Denis McGarry (11), Roger also became interested in the potential injurious effects of chronic exposure of the pancreatic islets to hyperlipidemia, which he termed "lipotoxicity" in a seminal review article published in 1995 (5). This became a major area of interest that he pursued for the remainder of his career. He was ahead of

his time when he proposed that fatty acids may exert their cytotoxic and proapoptotic actions through conversion to ceramides (12). Also during that period, a critical physiologic regulator of tissue lipid storage emerged with the discovery of leptin by Jeff Friedman in 1994 (13), and Roger was among the first to demonstrate the dramatic "lipid melting" and antidiabetic effects of recombinant leptin delivered by adenovirus vectors (14). Using this approach, he also demonstrated that complete depletion of the normal supply of islet fatty acids by chronic leptin therapy caused abrogation of insulin secretion in response to glucose and all other physiologic stimuli (15). In more recent years, he demonstrated an insulin-like action of leptin to lower blood glucose levels in diabetes (16). This work eventually culminated with studies showing that the glucose-lowering effect of leptin is partially explained by its ability to decrease glucagon secretion from the α cell, creating a near-perfect arch back to his early-career studies on glucagon biology (6).

Roger was an elegant man, with old-world manners and a fine sense of style. He believed in and practiced civility at all times and thought that scientific success should be defined by peer recognition of a rigorous and substantial body of work. It would be fair to say that Roger was driven in his pursuit of scientific knowledge and was often deeply buried in thought about the puzzle *du jour* that he might be exploring. This led him to be historically and hilariously absent minded — as just one example, leaving his car running in the parking lot on more than one occasion as he wandered into the office in the midst of a scientific daydream! But he also had a wonderful, impish sense of humor, including at his own expense, and when he would do something absent minded (leaving a dinner wearing a colleague's suit coat of a different color was another example!), no one would laugh with more glee in the telling of the story than him. His unique intellect, gentle charm, and deep sense of wonder and delight about scientific discovery will be remembered and missed by all who knew and loved him.

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