RETROSPECTIVE

Donald F. Steiner MD, 1930–2014: Discoverer of proinsulin

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Donald F. Steiner, the A. N. Pritzker Distinguished Service Professor Emeritus in the Departments of Medicine and Biochemistry and Molecular Biology at the University of Chicago, died at his home on Tuesday, November 11, 2014. He was 84 years old and had been a member of the faculty since 1960. Don was elected to the National Academy of Sciences in 1973. He revolutionized our understanding of the chemistry and biochemistry of polypeptide hormones. His contributions to understanding the biochemical nature of insulin production with the discovery of proinsulin and the development of C-peptide measurement have had profound scientific and clinical impact on the diagnosis and treatment of diabetes.

In 1967, Don discovered that human insulin was produced as a single chain, which he termed proinsulin (1, 2). That chain was then cleaved to release the two-chain insulin molecule and a new peptide, the C-peptide. This insight solved the mystery of how the two chains of insulin, named A and B, become associated. The discovery of proinsulin was the first unambiguous demonstration of the posttranslational processing of a polypeptide precursor into the mature functional form of the hormone by specialized proteolytic enzymes. This discovery was unexpected in light of the prevailing assumptions that the A and B chains of the insulin molecule were separately synthesized and later joined. Don characterized the proinsulin processing pathway and identified and characterized proglucagon and prosomatostatin. These findings created a paradigm shift in our understanding of the biosynthetic pathway of peptide hormones.

The discovery of proinsulin established the field of protein-precursor processing, paving the way to understanding how many other peptide hormones—as well as neuropeptides in the brain and endocrine system—are made and processed. Don and his colleagues later discovered the larger precursor of proinsulin, which they termed preproinsulin. This was a major advance for the understanding of peptide and prohormone processing generally. Don's work also made major contributions to the understanding of the class of enzymes, termed prohormone convertases, that covert proinsulin to insulin along with other processing functions. His insights helped colleagues all over the world, as he traveled widely and was a frequent keynote speaker. Don had many collaborators throughout the United States, Europe, Japan, and Israel. He was an honorary member of the European Association for the Study of Diabetes.

The immunoassay that Don and Arthur Rubenstein developed for the C-peptide of proinsulin provided a critical independent indicator of insulin secretion, as further developed by Kenneth Polonsky and many others (3, 4). This immunoassay has become a standard tool in the diagnosis of insulin-secreting tumors of the pancreas and the evaluation of the success of islet transplants.

The discovery of proinsulin enabled the pharmaceutical industry to improve the purity of insulin preparations extracted from animals and paved the way for biosynthetic

Donald F. Steiner MD. Photo courtesy of the University of Chicago.

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human insulin production. The immunological characterization of the proinsulin molecule allowed the pharmaceutical industry to introduce improved methods of purification of insulin to yield monocomponent insulin, leading to insulin preparations that were less likely to provoke an immune response. Don and his colleagues demonstrated that proinsulin could be cleaved to mature insulin by combined treatment with trypsin and carboxypeptidase B, which became the basis for the industrial production of recombinant human insulin (5). His work enhanced the management of diabetes and created a better life for millions of individuals with diabetes worldwide.

Working with Arthur Rubenstein and Howard S. Tager, Don described the first mutations in the insulin gene associated with syndromes of mild diabetes and elevated circulating insulin. The first abnormal insulin is known as insulin Chicago (6). Don continued to make contributions to the understanding of insulin processing and mutant insulins, including those that cause severe neonatal diabetes (7–10). His group found the first mutation in the insulin receptor that affected the function of this important protein, and showed that proteolysis of the proreceptor is necessary for its signal-transducing activity (11). Don's contributions to understating how insulin binds to its receptor, a problem he found particularly fascinating, continued to this year, working with Shu Chan, Michael Weiss, and colleagues (12, 13). Don frequently took an evolutionary view and published studies with Chan, Seino, Bell, and others on the protein sequence and gene structure of insulin, insulin-like molecules, and other pancreatic islet proteins from a wide variety of organisms (14, 15).

Donald Frederick Steiner was born in Lima, Ohio, on July 15, 1930. He earned his Bachelor of Science in chemistry and zoology from the University of Cincinnati in 1952, followed by a Master of Science in biochemistry and a Doctor of Medicine degree from the University of Chicago in 1956. Don completed his internship at King County Hospital in Seattle, WA, followed by a residency and postdoctoral fellowship at the University of Washington, and was asked to join the biochemistry faculty at the University of Chicago in 1960. Don rose quickly through the ranks, becoming professor in 1968 and Chairman of Biochemistry in 1973. He served as Director or Co-Director of the University of Chicago Diabetes Research Center from 1974 to the present.

Don published nearly 400 peer-reviewed papers and has been cited more than 10,000 times. He was elected to membership in the American Academy of Arts and Sciences in 1972 and the American Philosophical Society, the United States' oldest learned society, in 2004. Don won numerous prestigious national and international honors and awards, including the Lilly Award and the Banting Medal from the American Diabetes Association, the Joslin Medal from the New England Diabetes Association, Israel's Wolf Prize, and the Manpei Suzuki International Prize for Diabetes Research, the largest financial award for diabetes research, which honors "those who have enlightened researchers in the field of diabetes around the world with their original and excellent scientific achievements." This summer he was awarded the University of Chicago Alumni Medal, the highest award of the alumni association, an award of which he was particularly proud.

In addition to his seminal contributions to science, Don had a profound impact at the University of Chicago, particularly on the diabetes program and the formation of the Kovler Diabetes Center. The broad implications of his discoveries of the pathways of insulin biosynthesis and secretion, and his broad scientific interests, placed the University of Chicago at the forefront of diabetes research and created a wonderful diabetes environment for the recruitment of faculty and the training of fellows and students.

Don loved music (cf. 14) and was an accomplished amateur pianist (he built a harpsichord in the laboratory) with a particular fondness for Bach. He shared a love of keyboards with his brother Phares Steiner, a professional organ builder, who passed away last year. Don was a strong supporter of the arts. He also was a passionate advocate for human rights and always engaged in the political process. Those of us who worked closely with Don learned a great deal from him about puns, biology, teaching, and human nature. He was an extraordinarily kind, gentle, and attentive person with a large circle of friends. Don always had time for his staff and colleagues, would answer questions at length and in depth, and was absolutely devoted to his University. He will be profoundly missed.

A memorial service is being planned for May 1, 2015.

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