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SIDNEY FREDERICK VELICK
1913–2007

A Biographical Memoir by
CARL FRIEDEN

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Biographical Memoir


CHEMISTRY
NUCLEI AND PARTICLES

SIDNEY FREDERICK VELICK

May 3, 1913–December 29, 2007

BY CARL FRIEDEN

SIDNEY F. VELICK WAS WIDELY RECOGNIZED for his research in protein biophysics and the development of fluorescence techniques. In his later years Sid would say that the engine was still running but the body was rusting out. On December 29, 2007, the body finally did give out and Sid died at the age of 94. But those 94 years were filled with many twists and turns before his final scientific work was established. It is surprising how many fields he touched—from early studies on parasites and the chemistry of fatty acids to protein analysis and turnover to biophysical, kinetic, and mechanism studies of enzymes and proteins. Much of what is written here about his early years comes from memories written by Sid himself. He loved to write. Although I was his postdoctoral fellow for two years and his associate for several more before he left Washington University School of Medicine for the University of Utah, much of the background of his life was unknown to me. He just never discussed it.

EARLY LIFE

Sid Velick was born in Detroit, Michigan. His grandparents had immigrated to America in the early 1880s, motivated apparently by the condition of Jews in Europe. They settled in Detroit, where his parents were born. His father, after graduating from high school, took a night school law degree, was admitted to the Michigan bar, worked in the Office of the Controller, City of Detroit, practiced in a law firm for a few years before he left it to join the family business, a scrap iron processing business, with his brothers. His father's life, however, was cut short when he was murdered in a robbery when Sid was 12. Soon after his father's death the scrap iron business failed and life became difficult. The family first moved from their house to an apartment, then to Oklahoma for a year to live with Sid's uncle and then back to Detroit. In spite of these difficulties Sid apparently did well in high school and found considerable pleasure in both writing and reading. However, he did need to take jobs to help support the family. A job he had during high school required riding street cars. He claims to have read Tolstoy's *War and Peace* and a number of other books while riding to and from that job. It is clear that he was a voracious reader. That passion for reading lasted throughout his life.

THE PATH TO SCIENCE

I have some five chapters in which Sid wrote in detail about much of his early life. According to those writings, he really felt that his career would be in writing, and he entered Detroit City College (later to become Wayne State University), the first of his family to attend college. Because of his interest in writing he became the editor of the feature page of the college newspaper. Based on conversations with a fellow student and without any intention of following a career in medicine he classified himself as a premed student. He therefore had to take a series of courses in chemistry and biology, which he did, apparently with ease. According to his account, an event occurred in a lecture and laboratory course in comparative anatomy. The instructor was particularly effective, and Sid had done well in examinations and dissections. When he received a C grade he assumed it was a mistake. The instructor said it was no mistake and that he did not want to encourage the progress of another Jewish abortionist. Although not particularly religious, Sid writes of a number of incidents in his early life about the discrimination he encountered in his Detroit neighborhood.

The courses at Detroit City College were sufficient to provide a real interest in science, and he graduated with a B.Sc. degree in chemistry. He obtained his Ph.D. from the University of Michigan in biochemistry in 1938 for work related to bile salt metabolism. Discussions with Werner Bachman, an organic chemist, and his laboratory experience allowed him to synthesize early intermediates for Bachman's eventual total synthesis of the steroid equilenin.

THE EARLY YEARS OF SCIENCE

After obtaining his Ph.D., he was told that Robert Hegner, professor of parasitology at Johns Hopkins University School of Public Health wanted a biophysicist to find out why malaria merezoites preferentially invaded reticulated red cells. Although ignorant both of malaria and of reticulocytes Sid decided that he could handle any biophysical problems that might be encountered. So he accepted the position and during 1938-1940 he was a research fellow in parasitology and research associate in biochemistry at Johns Hopkins. During that time he wrote to Eric Ponder, the director of the Biological Laboratory at Cold Spring Harbor, asking whether summer laboratory space was available. It was, and his collaboration with Ponder produced one of his first papers, "The fixed framework of reticulocytes produced by injection of phenylhydrazine," published in the *Proceedings of the Physiological Society* in 1940. The time in Baltimore led to two papers dealing with malaria, including the first paper with him as the sole author—"The respiratory metabolism of the malaria parasite, *P. cathemerium*, during its development cycle" (1942)—published at the age of 29. It is possible that this work led to his later interest in cytochrome proteins because the work involved measuring cytochome oxidase activity.

When Hegner became ill with inoperable cancer, Sid needed to find another position, and it was recommended that he go to Yale to work with Rudolph Anderson in the Department of Chemistry. He joined Anderson in January 1941. Anderson was known for his work on plant sterols and the lipids of the tubercle bacillus, and Sid's first job there was to isolate and characterize the lipids of *Phytomonas tumefaciens* with special attention to the fatty acids. During 1941-1945, he was a research fellow in chemistry at Yale and very well may have been asked to join the faculty. However, he accepted an offer from Carl Cori for an appointment in the Department of Biochemistry at Washington University School of Medicine in St. Louis. The Cori department, of course, was famous for work on glycolysis and enzymology, and Carl Cori was one of the leading scientists of the world (see Mildred Cohn's biographical memoir of Carl Cori published by the National Academy of Sciences in 1992, *www.nasoline.org*). Thus, it was an honor to be asked to join the faculty. In the meantime in September 1941 Sid married Bernadette Stemler of Seattle, whom he had met at Johns Hopkins, where she was studying medical illustration and in particular art as it could be applied to medicine. Their marriage combined interests in art and science and Bernadette writes that when Sid died she lost her best friend.

WASHINGTON UNIVERSITY

In 1945 Sid moved to Washington University as an assistant professor. While the work he did at Hopkins and Yale must have attracted Cori's attention, the work began to change as a consequence of his interaction with Carl and Gerty Cori. He became much more interested in the structure and properties of individual proteins leading to his groundbreaking work on the mechanism of enzyme action and on protein turnover in muscle. Without a doubt the period from 1947 to 1957 was the most productive time for Sid. During those years, his work encompassed primarily two areas: amino acid compositions and protein turnover and enzyme purification and mechanism.

AMINO ACID COMPOSITION AND PROTEIN TURNOVER

Following the Second World War, biochemists were just beginning to investigate the molecular properties of proteins. At that time nothing was known about amino acid sequences or even the amino acid composition of specific proteins. Starting in 1948, Sid published several papers determining amino acid composition primarily of muscle aldolase and glyceraldehyde-3-phosphate dehydrogenase (1948). But Sid became interested in the issue of protein turnover, which was an active field of study starting in the 1930s but had been slowed during the war years of 1941-1945 and hindered by finding the right system to study. On developing methods to purify and crystallize both aldolase and glyceraldehyde-3-phosphate dehydrogenase from the muscle of a single rabbit, he and Melvin Simpson undertook an investigation of protein metabolism after injection of a single dose of radioactively labeled amino acids. Using a single animal allowed this direct comparison. By isolating and purifying 11 amino acids from each protein they could compare the specific activity of each amino acid in one protein relative to the other. From these data they then determined the relative rates of turnover of the two proteins (1954). The surprising and important result from this experiment was that the specific activity of each amino acid in aldolase was almost twice that of the corresponding amino acid from the dehdyrogenase. The constant ratio meant that the two proteins were synthesized from the same pool of amino acid precursors and that the two proteins turned over at different rates. In a timed experiment he and Murray Heimberg demonstrated that the incorporation of amino acids into aldolase and phosphorylase was rapid (within two hours) (1954). These experiments were extended to a number of other proteins (1956, 1972). The results were the same except for myosin where he concluded that the subunits of myosin were synthesized independently with different rates of metabolic turnover.

ENZYME KINETICS AND MECHANISMS

Most investigators tend to stick to a single protein for an extended period but in the time that Sid was at Washington University, he explored many systems in addition to aldolase and glyceraldehyde-3-phosphate dehydrogenase. These included the properties of phosphorylase, alcohol dehydrogenase, lactic dehydrogenase, a microsomal cytochrome and cytochrome reductase (with Philipp Strittmatter), L-amino acid oxidase (with me), and the glutamic oxalacetate transaminase (with John Vavra). But it was clear that his primary interest was in the glyceraldehyde-3-phosphate dehydrogenase. Together with M. W. Slein, the Coris had isolated and crystallized glyceraldehyde-3 phosphate dehydrogenase from rabbit muscle. Sid found the protein to contain a tightly bound NAD (1948) and later with Jane Harting elucidated this enzyme's mechanism of action, an example of substrate-level oxidative phosphorylation. In particular, he was interested in the interaction of the coenzyme DPN(H) (now NAD(H)) with the enzyme having determined the stoichiometry of NAD binding to be two for four identical subunits (1953). In a seminal 1958 paper he explored the binding of these molecules to glyceraldehyde-3-phosphate dehydrogenase and lactic dehydrogenase using fluorescence polarization and resonance energy transfer (1958). At the time, it was postulated that free NADH in solution existed in a folded conformation. What Sid showed was that NADH appeared to exist as an extended conformation on lactic dehydrogenase but a partially closed conformation on glyceraldehyde-3-phosphate dehydrogenase. He came to these conclusions well before any crystallographic data became available and the later crystallographic data proved that differences do exist in the conformation of bound NAD to these enzymes (PDB:5LDH and PDB:1J0X for lactate dehydrogenase and glyceraldehyde-3-phosphate dehydrogenase, respectively). Furthermore, this work presented the first experimental evidence that a tryptophan to NADH energy transfer occurred. That observation has been critical even today for enzymologists (and protein chemists) who use the change in tryptophan fluorescence to measure ligand dissociation constants.

MY INTERACTION

After I completed graduate work at the University of Wisconsin, my adviser Robert Alberty suggested I apply to Sid as a postdoctoral fellow. I did and was accepted into his laboratory in 1955. By that time Sid had finished his work with protein turnover and had become interested in fluorescence as a method for understanding enzyme mechanisms. An early model fluorometer took up a good bit of space in its own room. On his suggestion, and based on collaborative studies he was doing with Philip Strittmatter on cytochrome b_5, I undertook a study of cytochrome C reductase. At the same time, however, I was writing manuscripts on enzyme kinetics.

Over the two-year period as a postdoctoral fellow, Sid and I published only one paper together. He felt he had no input into what I was writing and therefore I should publish without him. A consistent theme that runs through the life of Sid Velick was his modesty. His allowing me to publish alone was certainly an example of that. My most vivid memory of Sid at work is his walking up and down the hall, cigarette in hand, head down, and obviously thinking of the next experiment.

Sid and Bernadette were gracious hosts. Not only at their house in St. Louis but inviting my wife and me to their home in Salt Lake City and their summer home in Washington state. Sid, however, was a poor driver. Meeting us at the ferry to drive to their summer home, he immediately started to drive down a one-way street the wrong way.

THE UNIVERSITY OF UTAH

Sid went to the University of Utah in 1964, becoming only the second chair of the Department of Biological Chemistry. The move was filled with hope but also a lot of responsibilities. In his first year he gave all the lectures in the biochemistry course for first-year medical students. The administration had only given him half of what they nominally offered in terms of space and funding, so he had to recruit new faculty members who were willing to share a lab. The department remained small during Sid's tenure—about seven faculty members—and had only a modest research presence. Sid maintained a small lab and continued his work on glyceraldehyde-3-phosphate dehydrogenase (1972, 1973), but the demands of the chairmanship—dealing with a wide assortment of committees and with his daughter's illness—limited his publications. During this time, however, he spent time in both the laboratories of Manfred Eigen in Göttingen, Germany, and Ernst Helmreich in Würzburg. Colleagues in the department had great fondness for Sid and wrote admiringly of his using new techniques, his way of running the department, his prodigious knowledge of literature outside of science, and his learning how to ski, which he did into his 80s. In addition to his professional work, Sid had joined his wife, Bernadette, as cofounders in 1965 of the Chamber Music Society of Salt Lake City, which is still in operation.

DEALING WITH MARTHA'S ILLNESS

While in St. Louis, it became clear that Sid's daughter, Martha, had a serious mental illness. Martha was both a cellist and a pianist but was becoming increasingly withdrawn. This was a great concern to Sid and Bernadette, and it is likely that the move to Utah was prompted by Martha's illness. During their stay at Utah, a considerable portion of Sid's time was devoted to Martha. Motivated by the experience of their daughter, the Velicks cofounded the Utah Alliance for the Mentally Ill, which advocated extensive reforms in the treatment of serious mental illness and led to the establishment in 1986 of Alliance House in Salt Lake City.

"RETIREMENT"

Sid stepped down as chair of the biochemistry department in 1978. During his life, he had published slightly more than 50 papers. But his dedication to science was all-encompassing. Unable to fathom not being involved with science he approached Ray Gesteland who had just moved from Cold Spring Harbor to Utah and asked to be a postdoc in the lab. Gesteland writes,

> I was delighted—anyone with his experience and knowledge of Biochemistry would be a great influence on all of us, especially graduate students, because we were all molecular geneticists, most of whom never took biochemistry too seriously. So Sid learned how to use an Eppendorf pipet, run DNA gels and clone DNA fragments. He was particularly interested in genes in Rye. Sid contributed much more than his biochemistry expertise to the lab. His wry

sense of humor entertained everyone. He partook of all the lab extracurricular activities: The turkey bowl, a Thanksgiving football game no matter what the weather; Skiing outings where his cross country energy put us to shame; Ice hockey games (no pads of course); Lab parties where he (and Bernadette) carried on just like the rest of us. Needless to say, Sid enriched all of our lives both scientifically, culturally and socially.

During this time of acting as a postdoc in the Gesteland lab, Sid was elected (in 1981) to the National Academy of Sciences.

EPILOGUE

When Sid was nominated for the University of Utah Distinguished Research Professorship in 1974, many letters from respected scientists supported the nomination. Academy member Efraim Racker wrote, "There is little doubt in my mind that Sidney Velick ranks among the leading physical biochemists in the world." Others noted his originality and his ability to master new techniques, frequently noting that Sid was a "biochemist's biochemist." Nobelist and Academy member Carl Cori probably expressed it best. He wrote, "I have a high regard for him. In my opinion Dr. Velick has all the qualities of an outstanding scholar and research man. He is innovating and has opened up a number of important new areas of research. All his work is characterized by originality of approach and thoroughness in execution. I would think that he would be an ideal candidate." And so he was. Sidney Velick is survived by his wife, Bernadette Velick, and son, William F. Velick, M.D.

I WOULD LIKE TO THANK Bernadette Velick and Dr. William Velick for their comments and for providing me with the writings of Sid Velick about his early years. I thank Ray Gesteland and Dana Carroll for their comments. I am indebted to the University of Utah archivist for photos and to the Washington University School of Medicine archives for historical documents.

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