RETROSPECTIVE

Robert Letsinger: The father of synthetic DNA chemistry

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Bob and Dorothy Letsinger with Tupence.

On May 26, 2014, Robert Lewis Letsinger died after a slow, progressive loss of his health. He played bridge with his family on Saturday, slipped into a coma Sunday, and died Monday. Thus ended the life of one of the most remarkable and productive scientists of his generation. All who knew him will miss his warmth and humor, his quiet energy and enthusiasm for greeting life's challenges, and his ease in expressing gratitude for the life he had lived and was living in a given moment. Scientists will remember his clever, spot-on, and forward-looking insights on his scientific endeavors and also on the research of colleagues.

Born on July 31, 1921, Bob was the son of Reed and Etna Letsinger. The family, including a total of five children, lived in Bloomfield, IN, where his father and his grandfather were lawyers and respected leaders in the community. When he was a sophomore in high school, the family moved to Bloomington, IN. Among his many activities, he coedited the school newspaper with his then dancing partner, later his life partner, Dorothy Thompson. They were married in 1943 and together they raised a family of three children (Reed, Sue, and Louise, who died in 1968). The family enjoyed a close-knit relationship that served them well as the children moved onward toward life's adventures. As Reed stated in Bob's eulogy, "He seemed to have missed out on the gene that gives people the ability to complain. He taught me that whatever life gives us, we have a choice which experiences we focus on and which we don't, and he chose to focus on those parts of his life that he truly appreciated. This choice served him well. And because that's how he chose to live, his life truly was charmed."

I first met Robert Letsinger during my interview for graduate school at Northwestern. He told me how they were attempting to synthesize macromolecules on an insoluble support. This was an exciting new concept that had never been explored (1962), and I decided not only to choose Northwestern University but also to work with Bob. Upon

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my arrival, I immediately joined Bob's laboratory and learned that Milt Kornet had synthesized a dipeptide on a polystyrene support. However, about one month later, our celebrations of this momentous event quickly turned to disappointment, as R. Bruce Merrifield published his tetrapeptide synthesis, also on polystyrene, in the *Journal of the American Chemical Society*. (Neither knew that the other had embarked on the development of this concept.) Milt and Bob quickly wrote up their synthesis, and it was published the same year, also in the *Journal of the American Chemical Society*. However, only Bruce Merrifield was recognized with the Nobel Prize, which was a great disappointment, as we believed that Bob Letsinger should have shared this honor.

Bob continued to carry out research in polymer-supported synthesis but not in the peptide field. Instead he switched to synthesizing DNA. In 1965–1966, while working with a postdoctoral associate, V. Mahadevan, they developed the first method for synthesizing DNA on an insoluble polymer. Bob's research led to a completely new procedure for synthesizing oligonucleotides that became known as the phosphotriester method. This approach quickly came to dominate the field and led to the synthesis of the genes for somatostatin, human insulin, and human growth hormone—the first bioengineered genes. The products of these genes led to Genentech's early success and the birth of the biotechnology industry.

In 1975, Bob Letsinger published the first synthesis using phosphorus III synthons for preparing DNA. At the time this was an important new concept, never before conceived in the nucleic acid field. His early papers provided a very convincing roadmap for further research as the yield per synthesis cycle was unprecedented, and the condensation reaction was complete in 5–10 min. All of us in biology, biochemistry, and biotechnology owe a great debt to Bob for showing us the way to preparing DNAs and RNAs that are used universally for many breakthrough discoveries in these fields.

More recently and while being the Clare Hamilton Hall Emeritus Professor at Northwestern University, Bob collaborated with Chad Mirkin to develop the use of DNA embedded on gold nanoparticles as a new, highly sensitive DNA diagnostic reagent. As a result of these discoveries, Chad and Bob founded Nanosphere, a biotechnology company focused on the direct detection of infectious diseases and other targets.

Although his research with nucleic acids clearly represents his most highly recognized achievement, Bob's breakthrough discoveries did not begin in this field. During and following World War II, Bob's research toward a PhD was with Avery Morton at Massachusetts Institute of Technology. His thesis research included the development of one of the early methods for preparing synthetic rubber. This polymerization procedure became known as the Alfin (alcohol + olefin) process and is still used today under special conditions.

In 1950, an historic milestone for sp^3 hybridized carbanions was set by Letsinger, who succeeded in the preparation of 1-methylheptyllithium as the first chiral, nonracemic alkyllithium (or any other organometallic compound). Enantioselective organometallic reagents, especially those containing lithium, continue to play a pivotal role in organic chemistry, academia, and industry alike.

Although I learned an enormous amount of chemistry from Bob, he excelled in many other ways that I have tried to emulate. For example, he showed me how to be a good teacher and how to motivate students in a positive and productive manner. Over the years, as I observed how others direct their programs, I consider myself one of the most fortunate of graduate students. Somehow, I found a mentor who was patient, who allowed students to explore their potential, and who focused his research on extremely challenging problems. Bob was foremost a teacher. For all who knew him as a lifelong friend or mentor, he taught us how to do good science and to enjoy the path it created for each of us.