Paul C. Zamecnik, senior scientist at Massachusetts General Hospital and professor emeritus of oncologic medicine at Harvard Medical School, was among the most important biochemical scientists of the 20th century. He passed away Oct. 27, 2009, at the age of 96.

Paul received his undergraduate degree from Dartmouth College in 1933, majoring in chemistry and zoology. He obtained his medical degree from Harvard Medical School in 1936 and followed it with internships at Huntington Memorial Hospital in Boston and Lakeside Hospital in Cleveland, Ohio. During his Lakeside Hospital internship, Paul was awarded a Finney-Howell Fellowship and a Moseley Traveling Fellowship to go to the Carlsberg Laboratory in Copenhagen, where he worked with Kaj Linderstrom-Lang. After he returned to the United States, Paul worked at the Rockefeller Institute for Medical Research in New York for two years, studying protein synthesis with Max Bergmann. He returned to Cambridge, Mass., in 1942 to join the faculty of medicine at Harvard Medical School and established his laboratory at Massachusetts General Hospital.

At Harvard, Paul worked with Fritz Lipmann, and the pair subsequently shared the Massachusetts General Hospital’s Warren Triennial Prize for their seminal study on the mechanism of action of clostridium α-toxin. In 1956, Paul became the Collis P. Huntington professor of oncologic medicine at Harvard Medical School, and he remained in that position until his retirement in 1979, after which he continued at the Worcester Foundation for Biomedical Research.

In the 1950s, Paul elucidated, through the development of cell-free systems, the biochemistry of protein synthesis. He and colleagues Philip Siekevitz, Robert B. Folkfield, Mahlon Hoagland and Mary Stephenson showed that ATP is necessary for amino acid activation leading to peptide bond formation, which, therefore, is not a reversal of proteolysis. They discovered transfer RNAs and showed that the linkage of amino acids to these small RNAs was the penultimate step of polypeptide synthesis. Paul’s group was also the first to identify the ribosome as the site of protein synthesis.

After that breakthrough, Paul continued to perform outstanding research. His RNA sequencing revealed that Rous sarcoma virus RNA has a 3′-OH tail of poly(A) bounded by a sequence that is identical to one at the 5′ end, suggesting that a cDNA-mediated circularization might occur during reverse transcription. A 13-mer oligodeoxynucleotide complementary to the terminus of RSV inhibited both the translation of viral mRNA in a cell-free system and virus replication. He showed that inhibition depends on both the ability of deoxynucleotides to enter intact cells and on Watson-Crick base pairing. His pioneering studies on antisense DNA and its inhibitory activity arose from that work. Antisense oligonucleotides immediately became important research tools for experimentally silencing gene expression. Those papers launched the era of antisense DNA. He applied those concepts to medicine, targeting the tuberculosis bacterium and the defective cystic fibrosis gene. Paul is regarded as the founder of the antisense therapy field.

Paul’s wife of 69 years, Mary Connor, died in 2005. He leaves daughters Karen Pierson and Elizabeth Coakley, son John, seven grandchildren and two great-grandchildren.

Paul’s major “side interest” was the company and conversation of interesting people. He learned to ski at Dartmouth and enjoyed skiing every winter. He was a good swimmer and tennis player. Later in life, he and Mary went to St. John in the Virgin Islands, where he loved to swim and snorkle. When he no longer partici-
pated in sports, he enjoyed watching football, basketball and tennis and knew all the players and their quirks.

On a personal note, my first correspondence with Paul led to his pointing out that I should spell his name correctly, but he forgave me for that. In recent years, we discussed science and enjoyed evenings dining at his club, the Somerset, in Boston. A word that characterizes Paul is devoted: As a scientist, he was devoted to ideas and his research, and, as a person, he was devoted to his friends. He was a true gentleman — friendly, sincere and straightforward.

Paul will be sorely missed by friends and colleagues, several of whom have provided reflections below.

By the 1970s, I had come to know Paul Zamecnik from various RNA meetings, and, in 1979, I suggested we collaborate to use psoralen-mediated nucleic acid cross-linking in living cells (which my lab had perfected) to prove to skeptics that his antisense oligodeoxy-nucleotides that were inhibiting translation were indeed doing so via hybridization with mRNA. We didn’t do the experiment and, in retrospect, I suspect he had not been as bothered by the “skeptics” as I had been, which says much about his legendary determination and confidence in his results.

Our years as colleagues at the Worcester Foundation (1979–1997) were delightful. In early December each year, he would send me a handwritten note with the expressed “hope” that I (the director) would not mind if he and his wife took a short holiday vacation. Being Paul’s “boss” was a comical situation that amused us both, but those notes were so typical of his manner (and manners). He was a persistent fountain of ideas to us all, a caring mentor to young faculty, a delightful lunchtime raconteur and, of course, a living history of science textbook.

Blessed with extraordinary prescience, Paul Zamecnik was an experimentalist of uncommon talent who transformed the modern era of biochemistry. That he was also a gentleman brought the two strands of his being into helical harmony.

I knew Paul Zamecnik for most of his scientific career, but my closest interactions with him occurred after he returned to the Massachusetts General Hospital and its cancer center in 1997. We discussed his ongoing research about applying the antisense technology that he developed years earlier. He was using in vitro systems to repair the genetic mutation in cystic fibrosis, to block cell wall synthesis in Mycobacterium tuberculosis and to target antibiotics to specific ribosome sites.

In some of our conversations, he reflected on the times after he discovered tRNA and lamented that he probably should not have taken time off in the early 1960s for a sabbatical with Sir Alexander Todd in Cambridge. When he returned to Boston, he found that the scientific floodgates had been opened by many others, including Marshall W. Nirenberg, Heinrich Matthaei, Robert W. Holley and Har Gobind Khorana. He told me, “I felt as if I was left standing on Mont-Saint-Michel while the incoming tide roared past me.”

I visited with him frequently in his final days and hours. Even as the curtain was falling, his utterings included phrases such as “Shine-Delgarno sequences” and “ribosome-binding sites.” Paul Zamecnik was a remarkably kind, generous, gracious and humble person whose greatest pleasure was scientific discovery.

Kurt J. Isselbacher
Distinguished Mallinckrodt professor of medicine
Harvard Medical School

The Massachusetts General Hospital found room for Paul Zamecnik for more than 20 years in the ‘60s and ‘70s. In an enclave in a research building, Paul and his group did their diligent work on cell-free protein synthesis, on the ribosome and transfer RNA, and on other major insights of the early molecular era. Although their laboratories were in a nonclinical area, the scientists could only reach it by passing through the Bulfinch Building, the heart and home of the medical service. This guaranteed interaction and consultation between true basic scientists and the clinicians trying to cope with cancer and similarly poorly understood disorders, and mutual enlightenment was inevitable. The geographical propinquity correlated with Walter Bauer’s design of keeping basic scientists and clinicians working together. And it succeeded because of Zamecnik’s medical training, his prior clinical experience in a cancer hospital, his scientific brilliance and his approachability.

Daniel D. Federman
Carl W. Walter distinguished professor of medicine
Harvard Medical School

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