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PAUL C. ZAMECNIK
1912–2009

A Biographical Memoir by
THORU PEDERSON

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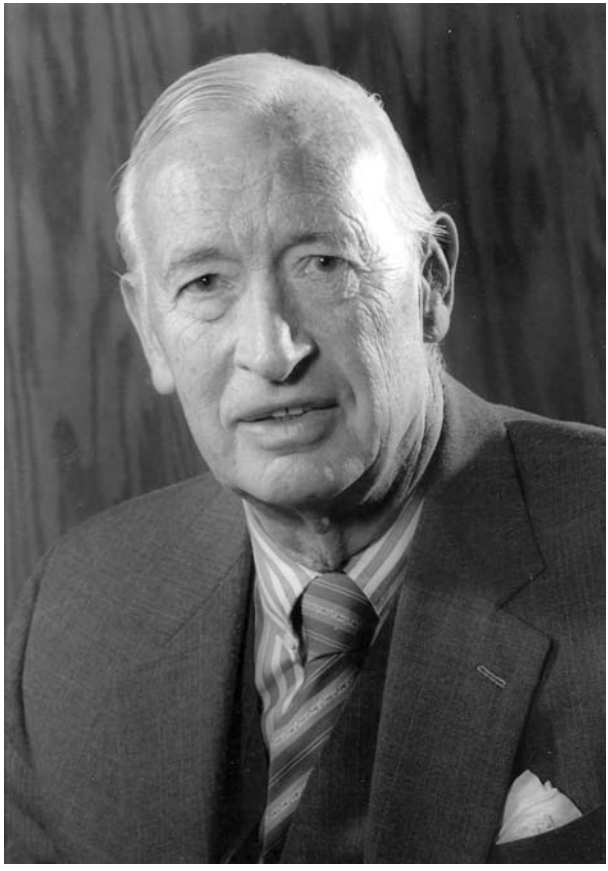
Biographical Memoir



Paul Jamecaire

PAUL C. ZAMECNIK

November 22, 1912–October 27, 2009

BY THORU PEDERSON

Though Paul Zamecnik never thought of himself as a molecular biologist, he played a major role in shaping the field and was held in high esteem by its members. After beginning his career in medicine (he still visited the wards and saw patients far into his laboratory career), he taught himself to do research and made seminal contributions to the understanding of protein synthesis including the discoveries of transfer RNA and of antisense DNA.

In person he was a delightful man, combining uncommon gifts as a storyteller with a good-natured open-mindedness for the views of his compatriots. It is doubtful that any scientist of his era was referred to as a "gentleman" more frequently than he. On the occasion of a birthday party for him at the St. Botolph Club in Boston, I remarked that we were honoring him in "midcareer" (close to being true as it turned out) and then handed the microphone over to Herman Kalckar. He began his remarks by saying, "One morning a woman came through Mass General's front door just when I did and asked me to direct her to Paul Zamecnik. I pointed her in the direction and said to just look for Maurice Chevalier."

Paul Zamecnik was born in Cleveland, Ohio, on November 22, 1912. I once asked him what the Czech family name meant and he said one translation is "one who holds keys to the

castle" (many meanings there). His father was a banker and his grandfather was an accomplished musician, composer, and conductor. Shortly after his high school graduation at 16, Paul and friends, all accepted at Dartmouth College, drove east together to start their undergraduate careers.

Dartmouth was in those days an automatic undergraduate pipeline for Harvard Medical School, to which Paul transferred in 1933. Upon graduation in 1936, he spent two years as a resident in medicine at Harvard's Collis P. Huntington Memorial Hospital and then took an internship at Western Reserve University Hospital in Cleveland, a step chosen because his mother was ill at the time. A seminal event in his nascent career occurred one day on the medical service at the latter institution when Paul saw a morbidly obese woman who had been admitted. While her workup got underway, he pondered why the body would necessarily shift its gears to adipose production as opposed to protein. While still in his internship, Paul took the train from Cleveland to New York City to visit Max Bergmann at the Rockefeller Institute. Bergmann had been the last student of a luminary of German biochemistry, Emil Fischer, and he was at the time one of the few biochemists in the world investigating protein synthesis from a chemical, as opposed to physiological, perspective. Bergmann said he took only organic chemists into his lab but might reconsider if Paul were to acquire such training.

As it turned out, Paul had a trump card to play. This moment was such a key turning point in the young Zamecnik's destiny that it is worth hearing him describe it himself (also to gain a sense of his elegant writing style).

> My admirable chief, Dr. Joseph Aub, in whom the golden rule had crystallized and the director of Harvard's pioneer Huntington Memorial Hospital for Cancer Research, recommended me to his friend, Kai Linderstrom-Lang, Carlsberg's multitalented new director, who accepted me without further questions for the years 1939-1941 (Zamecnik, 2005).

Paul's tenure in Copenhagen was transformative. He immersed himself in the intellectual ambience of the Carlsberg Laboratory and in collaboration with his wife, Mary (who was his skillful lab partner-assistant through most of his career), undertook innovative studies using the ciliate protozoan *Tetrahymena*, the attractive system for cell physiology that had been pioneered there by Erik Zeuthen. The training in organic chemistry Bergmann had demanded was not on the agenda but protein biochemistry permeated the place. Fritz Lipmann had left for America just a few weeks before Paul arrived (their two ships perhaps almost passing in a "counter-current" of pioneering protein synthesis to come). At Carlsberg, Paul also encountered Oliver Lowry, visiting from Harvard University, as well as another young American who arrived shortly: Christian Anfinsen. But Paul's research program came to a prompt end with the Nazi invasion of Denmark in April 1940. In the aforementioned autobiographical piece (Zamecnik, 2005) Paul described in riveting detail these months and his and his wife's departure and byzantine journey back to the United States. At its conclusion the ironically named S.S. *Manhattan* delivered them to a dock in the lower Hudson River estuary, and Paul knew the next stop on this journey. It was not far, right across town: the laboratory of Max Bergmann. This time the outcome was different; Paul was offered a position to commence as soon as new lab space would be ready. Time and a "side reaction" in Denmark had somehow changed the equilibrium, even though the requested training in organic chemistry had not been consummated. After another year at Mass. General, Paul at last went to Bergmann's lab.

Despite Paul's well-reasoned earlier perception that a sojourn with Bergmann would provide him with insights about the biosynthesis of proteins, this group's major achievement to date had concerned the dipeptide site specificity of proteo-

lytic enzymes. The requirement of energy for peptide bond formation had been noted by Henry Borsook at Cal Tech and by others, but at the time Paul came to Bergmann's lab the focus there was still chemical peptide synthesis on the one hand and continuing studies of proteolytic enzymes on the other. The question of how metabolic energy got plugged into biological protein synthesis was not on the agenda.

Upon returning to Mass. General, Paul collaborated with members of Joe Aub's group and others in studies of shock, and coauthored an impressive suite of papers in short order. At this time he also collaborated with Fritz Lipmann and Lydia Brewster on *Clostridium* toxin, leading to seminal advances (Zamecnik et al., 1947; Zamecnik and Lipmann, 1947) for which the three of them shared the coveted John Collins Warren Triennial Prize in 1946. Paul would go on to win the Warren Triennial Prize two more times.

In the late 1940s Paul's star was rising as a research leader, and he and his collaborators published a number of prescient papers on protein synthesis but in the context of metabolism and what was then called physiological chemistry, not biochemical mechanism. By 1949 he had become convinced that metabolic studies in tissue slices (a respected system at the time despite how archaic the term looks today) were severely limited. His group therefore turned their attention to tissue homogenates, notably of rat liver. They were in close contact with Nancy Bucher who was perfecting the art of rat liver homogenization in her studies of cholesterol biosynthesis. At this time, word was also getting around that Robert Loftfield, the first Ph.D. student of Harvard's renowned chemist Robert Woodward, had synthesized C^{14}-labeled alanine and glycine (Loftfield, 1947). Paul promptly entered into collaboration with Loftfield, which needless to say changed everything. In due course Phillip Siekevitz and others in Paul's lab refined a rat-liver-derived cell-free system that displayed convincing

incorporation of C^{14}-amino acids into protein. At this time other groups were also observing cell-free "incorporation" of amino acids but to his credit Paul saw that the key issue was to demonstrate that the labeled amino acids ended up at internal sites, as opposed to some end-addition reaction on endogenous proteins in the system. He had met Stanford Moore and William Stein when he was at Rockefeller with Bergmann more than a decade before and, prompted by this recollection, employed their starch column chromatography of tryptic digests to demonstrate that the C^{14}-amino acids had been incorporated at internal sites in the polypeptides whose elongation had occurred in his system.

One of the first major achievements of Paul's group at this time was the demonstration that the microsomes were the sites of amino acid incorporation in the cell-free system (Littlefield et al., 1955). The microsomes (vesicles in the homogenate that are derived from the rough endoplasmic reticulum) were known to be RNA-rich, and RNA had long been correlated with the protein synthetic activity of cells, notably in studies by the Swedish cytologist Torbjörn Caspersson and the Belgian embryologist Jean Brachet. The group of Henry Borsook had recently noted the preferential incorporation of amino acids into the microsome fraction, and now Paul's group took the additional step of demonstrating that the sites of this incorporation within the microsomes were the ribonucleoprotein particles, and that these particles (soon named "ribosomes" by Richard Roberts of the Carnegie Institution of Washington) were also the site of incorporation in vivo (Littlefield et al., 1955). This was a major heuristic advance in that it brought lingering suspicions of a link between RNA and protein synthesis into the domain of formal biochemistry.

One day in October 1955 Paul got to wondering if his cell-free protein-synthesizing system might be synthesizing

RNA. As mentioned above, it was known that the microsomes contained RNA, but no other RNAs involved in protein synthesis had been discovered at that time. Using solely the 100,000 x *g* supernatant fraction of the system, Paul added to one tube not a labeled RNA precursor (as he had added to the others) but a C^{14}-amino acid. This was in his attempt to perform a negative control, since the supernatant fraction being examined did not have protein synthesis activity. But to his surprise the C^{14}-amino acid became incorporated or attached to something in this supernatant fraction. Paul pondered this finding but did not immediately pursue it (Rheinberger, 1997).

Two years earlier, in 1953, Mahlon Hoagland had joined Paul's lab, following a stint in Fritz Lipmann's lab (Pederson, 2011). Lipmann had envisioned 12 years earlier, in a prescient article (Lipmann, 1941), that certain groups such as amino acid carboxyls might be prepared for subsequent biosynthetic condensation steps by ATP-dependent activation. Hoagland stepped into the fertile ground of Zamecnik's lab from this ideal training, inherited the immediately available cell-free system and soon discovered the amino acid activation step of protein synthesis, in which ATP participates in an enzymatic formation of adenylate anhydride bonds with amino acid carboxyl groups (Hoagland, 1955; Hoagland et al., 1956). Lipmann's lab upstairs quickly shifted gears and got into the chase (Davie et al., 1956) but it was too late; the discovery's priority had gone to Hoagland and Zamecnik. Meanwhile, Paul suggested to Hoagland that he take up the curious observation Paul had made (*vide supra*), namely that a C^{14}-amino acid becomes linked to something in the 100,000 x *g* supernatant fraction of the system. In short order Mahlon and Elizabeth Keller discovered that the amino acid was being attached to RNA of low molecular weight. The Zamecnik lab had discovered transfer RNA (Hoagland et al., 1958).

This was the "adaptor" for getting the language of DNA into protein that Francis Crick had brilliantly anticipated. Crick once told me that hearing of Hoagland's and Zamecnick's discovery was one of the highest moments of his life in science. In contrast, Paul had not given Crick's anticipation of the discovery much note, being a conservative in such matters and preferring to await hard data. We can note in passing, as many observers have before, that science is the better for having both kinds of participants.

His pathfinding work that had opened up protein synthesis to biochemical dissection and the monumental discovery of transfer RNA had now brought Paul Zamecnik to the full attention of the collateral guild of molecular biology, of which he had not been a member. He and his talent had been known early on to many in that discipline, but he was not known throughout the branches of molecular biology descending from protein structure and bacteriophage genetics, the two defining arms. But by the late 1950s and most definitively into the early 1960s, Paul Zamecnik and his work began to be noticed and admired across both biochemistry and molecular biology.

A signature feature of Paul's epochal work in the 1950s and 1960s was the unusual way he populated his lab. Because it was on the other side of the river from the main Harvard campus, graduate students were not the mainstay. But neither were just graduated Ph.D.s In fact, Paul did not typically take a freshly minted Ph.D. He fixed his sights instead on able scientists who were a bit further along, sometimes much further—ones whose mentors were people he admired or whose early stage career momentum gave him optimism. He also believed in the happy incubator model in which a productive research lab can have a number of talented people working with only light touches from the orchestra leader. He had observed such a motif at the Carlsberg labo-

ratory and again under Joe Aub's gentle leadership. It is to be noted that among all his very many significant influences over a long career, about whom he always spoke with appreciation, Paul's sense of indebtedness to Aub was the most enduring. A memoir he published after Aub's death (Zamecnik, 1974) is one of his finest pieces of writing ever, and this from a man who was an uncommonly gifted writer in the first place—for all audiences.

In the 1970s Paul began thinking about how it might be possible to interrupt protein synthesis by sticking a complementary piece of nucleic acid onto the mRNA. He got to this notion in a way that could constitute a good case study for a Ph.D. thesis in a history of science program. Paul had by this time shifted most of his lab to the study of viral nucleic acids and in due course began, with his colleague Dennis Schwartz, to sequence in from the 3′ end of Rous sarcoma virus RNA. Using an expression he so often loved to recite later (and this is a paraphrased amalgam of various accounts he published or gave in lectures): "Meanwhile, across the river Bill Haseltine, Allan Maxam and Walter Gilbert had a new method and got far in from the 5′ end in only weeks, while we had been ever so slowly whittling away from the other end." The publications of the two groups came out back to back by cordial agreement (Haseltine et al., 1977; Schwartz et al., 1977). As Paul always emphasized, the point was not the huge discrepancy in sequencing speed (though he long thereafter entertained audiences with his bemused account of it, with clear admiration for the other group's accomplishment) but that the 3′ end sequence he and his colleagues determined was the same, and in the same polarity, to that found by the Gilbert lab. Both groups realized that such a sequence arrangement would mean that when reverse transcriptase synthesized the complementary DNA strand, its 5′ end would be complementary to the template RNA's 5′ end

and thus might circularize with it. Given this, Paul got the idea that interfering with this presumed base pairing might be a novel way to think about blocking retroviral replication. The related idea of trying to inhibit the translation of a specific messenger RNA by a complementary nucleic acid had been suggested earlier by Alex Rich's lab based on in vitro results (e.g., with a cDNA complementary to a very long stretch of the message), but this seemed unlikely to hold therapeutic potential given the long DNA used. At this time in Paul Zamecnik's career, as throughout it, one must bear in mind that to a very significant degree he was also still thinking as a physician. In his post-protein synthesis era, as seminal as those discoveries had been, he wanted to turn this avenue of science toward patient treatment.

In 1976 Paul contracted with a company he had previously helped form, Collaborative Research, in Waltham, Massachusetts, to synthesize a 13-mer oligodeoxynucleotide complementary to the terminal repeats in Rous sarcoma virus RNA. These were early days in the chemical synthesis of DNA (and RNA) and by good fortune the chemist at the company into whose hands this contract fell had trained with Gobind Khorana. Paul and his longtime colleague Dr. Mary Stephenson soon published back-to-back papers reporting that this oligo inhibited the synthesis of viral proteins in a cell-free translation system (Stephenson and Zamecnik, 1978) and also blocked replication of the virus in infected cells (Zamecnik and Stephenson, 1978). Paul named the oligo a "hybridon." The two papers Paul and Mary Stephenson published launched the concept, and era, of antisense DNA. Years later when we were institutional colleagues (*vide infra*), Paul recalled to me how the reprints of these two papers had "turned yellow on our laboratory shelf." It is true that there were doubts. The inhibition of RSV mRNA translation was seen by some as an anticipated result and the more relevant

in vivo inhibition of viral replication generated skepticism in some quarters as to drug development economics.

Antisense DNA was in utero and oxytocin pulses were just starting to induce its birth when another major event occurred in Paul Zamecnik's career. It was 1977, and at 65 he found himself up against Harvard Medical School's strict rule, viewed as draconian by some including Paul, forcing retirement at that age. (This rule had caused Harvard to lose Fritz Lipmann, shortly before he won the Nobel Prize.) Though I was never part of the Harvard system, I thought this policy was absolutely nuts as did many other Crimson *auslanders* at the time. Many years later Paul showed me the appeal letter he sent to the dean, a masterpiece of exposition and suasion. But it was turned down, and so Paul arranged to spend a year at the National Institutes of Health as a Fogarty visiting fellow. There he refined his thoughts about antisense DNA and considered his options. As the Fogarty year was closing Paul wrote to his former colleague Mahlon Hoagland, then president and scientific director of the Worcester Foundation for Experimental Biology, in Shrewsbury, Massachusetts. In this letter Paul outlined his vision for a research program on antisense DNA as a novel therapeutic approach to a wide array of diseases. As could have been anticipated, Hoagland was not unreceptive. When Mahlon showed me Paul's write-up I thought it read both as a cogent research plan and a passionate novella. (Years later I uncovered in my files a photocopy Paul had sent me, of his cover letter accompanying his write-up to Hoagland. It ended: "Of course, this proposal reads like a novel.")

Paul joined the faculty of the Worcester Foundation in 1979 and a few years later received a contract from the National Institute of Allergy and Infectious Diseases to develop an antisense DNA strategy for inhibiting HIV. Subsequent funding from the Mathers Foundation also helped carry this

work forward in its "not ready for prime time" era as regards how NIH study sections would have likely viewed a standard grant application. Paul and I always valued the courageous decision the Mathers Foundation took on antisense DNA, and on him.

Antisense DNA proved challenging to convert from a gene knockdown tool (great utility there to be sure) to a pharmaceutical reality. Oligodeoxynucleotides were found to possess unattractive pharmacokinetic and bioavailability properties and the first generation of modified oligos, the phosphorothioates, stuck to many other molecules in the bloodstream. Nonetheless, Paul properly recognized that drug development is always a longer road than usually first imagined, and in 1990 he and the Worcester Foundation started a company, Hybridon Inc. Based on his own previous studies, Paul and the company chose HIV as the major target and over the next several years Hybridon managed to move a candidate compound into preclinical studies and even an early-stage trial in patients. The entire experience of Hybridon was a revelation to Paul and the rest of us who were involved. He was surprised and dismayed by the skepticism of many venture capital and pharmaceutical executives, some of whom had previously been Harvard Medical School students or colleagues he had known. As president of the Worcester Foundation I accompanied him on many of these trips. One time we visited a venture capital firm in New York City and as we were about to enter the conference room we saw half a dozen 25- to 30-year-olds sitting around the table, with their freshly sharpened no. 2 pencils and yellow tablets at the ready. Paul whispered, "Thoru, they are young enough to be my grandchildren. And what do they know about RNA?" They indeed were that young, but they had read everything in the antisense field, and were well versed in drug development risks and challenges.

RNA now has taken the forefront as a nucleic acid-based therapeutic approach, and Paul watched over those developments with keen interest during the last 15 years of his life, always attuned to RNA science. I suspect he did so with a certain sense of déjà vu. Virtually every experience catalogued in the antisense DNA field was being seen again with RNA oligos, and every sugar and backbone modification developed in the antisense DNA era was, and is now, being tried, as the RNA therapeutics field passes through its very early days. Meanwhile, at the 2010 Cold Spring Harbor Laboratory meeting on oligonucleotide and antisense therapeutics, some of the clinical trials and preclinical research presented on oligodeoxynucleotide inhibition of pathogens, or correction of genetic mutations, were encouraging. At one session a tribute to Paul was held, and I put up a slide of his smiling face, which looked out onto an audience of colleagues who had long been inspired by him and deeply missed his presence.

In 1997 the Worcester Foundation merged with the University of Massachusetts Medical School. As president of the foundation I knew this was a good move (especially in my own field, RNA) and was pleased that almost all of the Worcester Foundation's able scientists would be coming along. But Paul decided to return to Boston and set up a lab near Hybridon's headquarters in Cambridge, where he continued to very productively investigate applications of antisense DNA, particularly for tuberculosis and for genetic correction of cystic fibrosis, as well as other projects (Zamecnik, 2005). Just as his wife Mary had so long worked beside him in the lab, in these later years their daughter Karen Pierson joined the lab and worked closely with her father. Paul's productivity continued undiminished, and subsequently he arranged an appointment at Massachusetts General Hospital, setting up a lab at the institution's new Charlestown campus. At that

happy moment two strands—one a visionary scientist of genetic mechanisms and the other one of America's vanguard research-based medical institutions—had now come back together once again, a reannealed RNA double helix.

In this account we have learned of Paul's career odyssey and major scientific contributions but have only tangentially addressed him as a man, though some of his persona may have already become evident. Though the term is overdeployed, there can be no exaggeration in characterizing Paul Zamecnik as a "gentleman," as was mentioned at the outset in Herman Kalckar's wonderful quip. Paul was calm and at equilibrium in his demeanor, always deployed a kind, mannered style and was found smiling in almost every moment when in the presence of others. He was patient when in the company of pedants or sycophants, did not rush to judgment about others, and had a keen interest in everyone around him. In those rare instances in a meeting or conversation where his viewpoint did not appear to be prevailing (and these occasions were indeed rare) Paul was fond of saying pleasantly, "Well, as a Harvard Medical School dean liked to say: 'We can agree to disagree.'"

A love of literature and poetry was often evident when in Paul's presence as he could recite Shakespeare and other writers with graceful facility, and always in just the right context (Pederson, 2009). John Stuart Mill said, "Genius is the ability to perceive analogies." I often found myself thinking of Mill's definition (as good as any) each time Paul would pull out just the perfect metaphor from his extraordinary memory bank when at a gathering. Another feature of Paul's personality was that he was very careful, and skillful, whenever he had reason to make a reserved remark about someone. It was as if saying something negative brought him dyspepsia. For example, one time I loaned him my copy of Joseph Fruton's autobiography, mentioning my view that it

was quite engaging in places but less so in others. A week later he returned the book with a note: "Dear Thoru, Thanks for this view of Fruton's book. Once, at a meeting in 1954, Linus Pauling said of Joe Fruton's efforts to explain protein synthesis on the basis of a modified reversal of proteolysis: 'Dr. Fruton, I am afraid you are trying to pull yourself up by your own bootstraps.' With best wishes, Paul." He may have had the same opinion on that aspect of Fruton's work but gave the role of skeptic to Pauling. While mentioning autobiographies, I also remember sharing with Paul a memoir by the microbiologist Bernard Davis. Although always on cordial terms, Paul and Bernie had experienced occasional disagreements in their years at Harvard Medical School, not over science but involving administrative issues of interest to Paul, in which Davis's fiscal conservatism had prevailed in ways that to Paul seemed unjust. After reading Davis's autobiographical essay, Paul sent me a note saying, "Thank you for sharing this, from which I now know Bernie better." Zamecnik had an open mind, always ready to receive new data and reorient a nascent opinion. And to complete this trilogy on his art of note writing as a mode of communication, there is the following example. Each December in the years he was at the Worcester Foundation, Paul would send me a note explaining that he and Mary would "again like to take a brief holiday trip to our place in St. John," adding the hope that "the President will be comfortable with this, especially as other members of the lab will be on hand throughout." In these gracious preholiday notes there was both a zephyr of comedy (after all, was this innocent request going to be denied?) but as well a sense that he felt, to some small degree, that obtaining permission was actually necessary. The key point is he was kind enough to send such a communication at all.

After leaving the Worcester Foundation, the years back in Boston were every bit as productive. Paul continued to work full time in his lab at Mass. General up to just a few weeks before his death, on October 27, 2009, from a recently diagnosed neuroendocrine tumor. He had up to then been in apparent good health and working at a lively pace, and indeed had been engaged with a manuscript only weeks before. He would have been 97 on November 22, 2009. Mary Connor Zamecnik, his wife of 69 years, had predeceased him by four years. They were as devoted a couple as one ever witnesses. He is survived by two daughters, a son, and several grandchildren and great-grandchildren.

Paul Zamecnik was elected to the National Academy of Sciences in 1968. He was also a member of the American Academy of Arts and Sciences and the Institute of Medicine. He held honorary doctoral degrees from Columbia University, Dartmouth College, Harvard University, Rogers and Williams College, and the University of Utrecht. He was the recipient of the James Ewing Award, Borden Award, Passano Award, and the John Collins Warren Triennial Prize of Massachusetts General Hospital an extraordinary three times: the aforementioned 1946 prize with Fritz Lipmann and Lydia Brewster, in 1949 with Mary Stephenson and Ivan Frantz, and in 1998 with Christiane Nüsslein-Volhard. In 1991 he was awarded the National Medal of Science, and in 1996 he received the second Albert Lasker Award for Special Achievement in Medical Science.

Paul Zamecnik's opening up of protein synthesis as a rigorous discipline in biochemistry stands as his scientific signature for all time, and is a cornerstone in the edifice of molecular biology. His gracious bearing, wisdom, and gifted storytelling enriched the lives of his colleagues and friends. Owing to his very long, active life, most readers of this memoir will have known him, or known of him, in his later career,

and so we might close with one of the favorite lines that he liked to use occasionally while still pushing ahead in his 90s, from Carlos Fuentes: "It is better to die in battle, than to lose one's memory or fall down the cellar stairs."

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