Paul Zamecnik, M.D., '34: Life's work

By Amos Esty

Grew up: Cleveland, Ohio

Education: Dartmouth College '33 (A.B.), Dartmouth Medical School '34 (B.M.S.), Harvard Medical School '36 (M.D.)

Training: Resident, Huntington Memorial Hospital, Boston, Mass.; intern, University Hospitals, Cleveland, Ohio; fellowship in protein synthesis at Carlsberg Laboratories, Copenhagen, Denmark

Marital status: Widowed since 2005, after 69 years of marriage to Mary Connor Zamecnik

Awards: At least six honorary degrees, including one from Dartmouth (1988); National Medal of Science (1991); Lasker Award for Special Achievement in Medical Science (1996); and many more

Little-known fact: Played the violin as a boy

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A three-decade scientific career is something to be proud of. Dr. Paul Zamecnik ought to know. He's logged not just one but two of them—one before and one since retirement. His first 30-year stint ended when he reached Harvard's mandatory retirement age in 1979. He didn't rest on his laurels but merely switched employers. Today, almost 30 years later, he's still working full-time and has no plans to stop.

A 1934 graduate of Dartmouth Medical School, Zamecnik (pronounced ZAM-ess-nick) can claim more than mere longevity. Early in his career, he rubbed shoulders with Drs. James Watson and Francis Crick, who won the Nobel Prize in 1962 for identifying the structure of DNA. And Zamecnik has continued to make important scientific contributions as the decades have ticked by. In 1996, he won the Albert Lasker Award—known as "the American Nobel"—for a career, according to the award citation, "characterized by sheer scientific originality and brilliance."

In the 1950s, Zamecnik helped unravel the mystery of how proteins are made—inventing the first cell-free system for studying protein synthesis and identifying transfer RNA. Two decades later, he pioneered antisense technology, a method of attacking harmful viruses and bacteria by blocking the expression of specific genes.

Today, as he nears his 96th birthday, he's still an active scientist at Massachusetts General Hospital (MGH); his current focus is developing treatments for tuberculosis. Some people, Zamecnik concedes, might think, "Why isn't that guy in a retirement home?" But Karen Pierson, one of his three children as well as a technician in his lab, has a simple explanation for her father's refusal to leave the bench: "He loves to work."

As a DMS student in the 1930s, Zamecnik had planned to go into clinical medicine. That would have been the safer choice, he admits. But then he discovered that he enjoyed research. Within months of Zamecnik's 1929 enrollment (at age 16) in Dartmouth College, the stock market crashed and the nation entered the Great Depression. "In a way I was blessed," he says. "I went through the Depression without being much affected by it because I was in school most of the time." He remembers spending a lot of time studying as both an undergraduate and a medical student, but he still managed to take advantage of the outdoor opportunities available in the New Hampshire mountains. He stayed at cabins owned by the Dartmouth Outing Club, and he provided medical assistance at one of the earliest downhill ski races in the country, on Mount Moosilauke.

It was during his second year at Dartmouth Medical School that Zamecnik first encountered scientific research. He tried to grow frog tissues in culture, following the lead of the renowned scientist Alexis Carrel, who ran a lab at the Rockefeller Institute in New York City. "He was a famous man in his day," says Zamecnik. "Won a Nobel Prize [in 1912]. Had his picture in the papers." In 1932, Carrel made headlines for keeping cells from a chick embryo alive for 20 years.

After finishing DMS's then two-year program, Zamecnik went on to Harvard to complete his M.D. In 1936, as he approached graduation, he applied for an internship in surgery at MGH. The problem was that just about everyone else in his class wanted the same internship. "So I found myself on a waiting list," he says.

Fortunately for Zamecnik, a Harvard instructor mentioned a residency in oncology at Huntington Memorial Hospital. Zamecnik met with the hospital's director, Dr. Joseph Aub, for an interview. But "instead of quizzing me about medicine and plumbing the depths of my ignorance," Zamecnik says, Aub asked the young trainee if he'd be willing to teach his daughters to ski—assuming that, as a Dartmouth graduate, Zamecnik must be a good skier. Despite his limited skills on the slopes, Zamecnik told Aub he'd be happy to oblige.

There was a strong commitment to research at Huntington, so Zamecnik had a chance to delve deeper into the world of discovery. "You didn't have many patients to care for," he says. "The [rest] of your time you were allowed to spend in the laboratory."

But after a year and half there, still thinking he'd ultimately practice medicine, Zamecnik began to worry that he needed more clinical training. So he and his wife, Mary, whom he'd married in 1936, moved to Cleveland, where he did an internship in medicine at Uni-

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JON GILBERT FOX

Zamecnik had his first experience with research at Dartmouth in 1934—and 74 years later, just shy of his 96th birthday, is still doing research full-time at Mass General.

versity Hospitals. He liked the internship and his colleagues but realized that he really did prefer research and that he didn't want to commit to a life split between the lab and the clinic. Practicing medicine "draws you in," he says. "It's your first priority."

Zamecnik was also motivated by the lack of medical knowledge at the time. "A medical doctor saw the patient, listened to his chest, banged him on the back a little bit, quizzed him, then blessed him and allowed the curative powers of nature to take over," he says. He thought he could make a greater contribution by advancing the science behind medicine than by treating patients.

So he took some time off from residency to attend biochemistry classes and began a small research project on the side.

Soon he became interested in a question that, years later, would lead to one of his most significant discoveries. During an autopsy on an obese woman who had died for no apparent reason, Zamecnik wondered why her body had so much fat and so little muscle and protein. He asked other doctors if they knew how proteins were made, but no one had an answer. One colleague, however, mentioned that a scientist at the Rockefeller Institute was studying protein synthesis. Zamecnik traveled to New York City and asked to join the lab but was told he didn't have enough experience doing chemistry research.

Determined to get that experience, Zamecnik applied for and received two fellowships to spend a year working with a leader in the field of protein chemistry at Carlsberg Laboratories in Copenhagen, Denmark. When the chief of medicine in Cleveland found out, he told a friend of Zamecnik's, "That young man is pouring his medical education down the sink." Zamecnik clearly relishes the remark—he's referred to it on many occasions over the years—and laughs as he notes that it "didn't worry me at all."

His stay in Copenhagen was cut short by Germany's 1940 invasion of Denmark; he ended up spending only seven months there. Even so, when he returned to the U.S. he was offered the job he wanted at the Rockefeller Institute. Two years later, he was appointed an instructor at Harvard Medical School and set up his own lab at MGH.

In the early 1950s, while Watson and Crick were figuring out the double-helix structure of DNA, Zamecnik was hot on the trail of how proteins were made. His invention of the first cell-free system—a combination of cellular components and amino acids that could synthesize proteins in a test tube—later played a role in breaking the DNA code.

Then in 1956, with two MGH colleagues—Drs. Mary Stephenson and Mahlon Hoagland—Zamecnik found that a small amount of seemingly useless RNA facilitates protein synthesis by carrying amino acids to ribosomes, organelles outside the cell nucleus, where they are pieced together to form proteins. This discovery, of what's now known as transfer RNA, explained how the language of DNA is converted into a sequence of amino acids.

There was at that time a growing sense of competition among labs and institutions as the molecular underpinnings of medicine were being elucidated. But the environment in Zamecnik's lab remained collegial, says Hoagland, who in the 1960s chaired DMS's biochemistry department. "Paul was a remarkable man," Hoagland says. "He was very generous in acknowledging the contributions of his peers."

In 1956, Zamecnik was appointed Harvard's Collis P. Huntington Professor of Oncologic Medicine, a title he held until reaching the school's mandatory retirement age in 1979. He then took a position with the Worcester Foundation for Biomedical Research in Shrewsbury, Mass., where he was reunited with Hoagland, the director of the foundation at the time. In 1997, Zamecnik left the foundation to become a senior scientist at MGH.

Zamecnik's current research makes use of antisense technology, a technique he developed in the 1970s to stop the expression of specific genes. The method works by preventing messenger RNA (mRNA) from functioning properly. Normally, mRNA carries the genetic information encoded in DNA to the ribosome, where that information is translated into specific proteins. Both DNA and mRNA are composed of strands of molecules called nucleotides; DNA has two strands—a sense strand and an antisense strand—while mRNA has only a sense strand. In 1978, Zamecnik showed that it's possible to create a short chain of nucleotides—a synthetic antisense chain—that

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in mice injected with human melanoma cells, inhibiting MMPs prevented the melanoma from metastasizing.

She also advises students, teaches, and gives talks. And she spends a lot of time writing and reviewing grants and papers, trying to impress on students and colleagues the importance of good writing. She's a very good writer herself. An article she wrote for the March 2002 issue of *Nature Reviews Molecular Cell Biology*—"Matrix metalloproteinases: a tail of a frog that became a prince"—is a compelling story of two scientists who discovered how tadpoles lose their tails . . . ■

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can bind to a complementary nucleotide sequence on the mRNA strand. The result is double-stranded mRNA, which is unable to translate genetic information into proteins. Zamecnik then used the antisense technique to stop the growth of a virus by blocking a gene essential to its replication.

Zamecnik "might be considered the father of antisense technology," says Dr. Marcus Horwitz, a tuberculosis (TB) expert at the University of California, Los Angeles. Horwitz has been collaborating with Zamecnik for 12 years to use antisense technology against *Mycobacterium tuberculosis*, the bacterium that causes TB.

The bacterium's nearly impregnable cell wall is an important factor in TB's virulence, so it is an obvious target for fighting the disease. In 2000, Zamecnik and Horwitz showed that it is possible to employ antisense technology to hinder the growth of the cell wall. By 2002, they had identified targets in the bacterium's genome that might be vulnerable to antisense therapy. They have continued to refine their approach and last year published an article reporting success in inhibiting the growth of *M. tuberculosis*.

Zamecnik says there's still progress to be made before the findings can be translated into effective treatments, but he thinks the goal is within reach. With so much work to do, he sees no reason to stop now. "As long as you can be competitive," he says, "you might as well do what you like." ■