

NORMAN H. HOROWITZ 1915 — 2005

Norman Harold Horowitz, professor of biology, emeritus, died on June 1. He was 90. “Horowitz was one of the pioneers of biochemical genetics,” said Caltech president David Baltimore at a memorial service held on September 12. “He helped put in place our understanding of the role of genes in the overall economy of the cell, which enabled people to go on and think about how genes can exert their action and be controlled in their action. His investigations established a paradigm on which all other work on genetic regulation was based.”

Born 1915 in Pittsburgh, Horowitz attended the University of Pittsburgh and graduated in 1936 with a

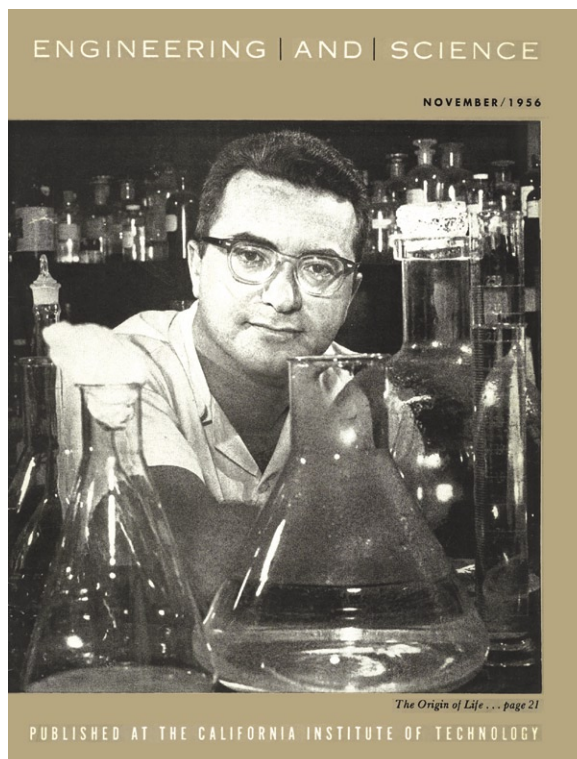


Horowitz made the cover of E&S in November 1956 when we published *The Origin of Life*, his historical account of man’s attempts to discover the fundamental characteristics of living matter.

bachelor’s degree in zoology, before coming to Caltech for his graduate studies. He wanted to do genetics research, but T. H. Morgan assigned him to work with embryologist Albert Tyler on the development of sea urchins and the marine worm *Urechis*. The trio spent their summers at Woods Hole, which is where Horowitz met his wife, Pearl Shykin, who was then at Radcliffe. They married soon after Horowitz received his PhD in 1939.

A one-year fellowship took him to Stanford to work on marine worm respiratory pigments with Douglas Whitaker, after which he returned to Caltech to work with Henry Borsook on tooth calcification.

In early 1941, George Beadle came down from Stanford to give a seminar about the genetics research he had begun with fellow biochemist Ed Tatum using the red bread mold, *Neurospora crassa*. Beadle had attended Tatum’s microbiology lectures at Stanford and learned that bacteria and fungi have the same biochemistry, but different nutritional requirements, recounted Horowitz in his 1984 Caltech Archives oral history. Fungi need growth factors, the fungal equivalent of vitamins. Beadle realized that if he could find mutants that couldn’t make a particular growth factor—because a biochemical pathway had been blocked—he could get an insight into the way the genes worked. He chose to use *Neurospora*, which could



make all its own growth factors bar one (which was added to the growth medium). If, as he believed, one gene made one enzyme, the loss of a gene could be shown by the loss of a growth factor.

Beadle and Tatum agreed to induce mutations with X-rays in a normal culture of the mold, “mate” it with an unirradiated culture, raise 5,000 progeny, and see which biochemical abilities they had lost; and if they didn’t find any mutants among these 5,000, they would give up. Fortunately, their first nutritional mutant was no. 299. It lacked the ability to make pantothenic acid, vitamin B₆.

Beadle’s seminar stunned the audience. And when he asked for a couple of post-docs to help him, Horowitz immediately signed up. “I’ve always felt that was the single most important decision of my life,” he said, “because working for Beadle was just marvelous.” Horowitz spent the rest of the war years at Stanford gathering evidence in support of Beadle’s one

gene—one enzyme hypothesis.

Speaking at the memorial service, Elliot Meyerowitz (Caltech’s Beadle Professor of Biology and chair of the biology division) reminded the audience that, in the mid-’40s, the hypothesis that one gene made one enzyme was viewed with great skepticism. It was generally thought that every gene contributed to a very large number of different biochemical processes: some genes made small peptides, and other genes made products that stitched these peptides together to make enzymes. As many as 100 genes might be involved in the production of one enzyme and, conversely, each gene might contribute peptides to the synthesis of many different enzymes. The results found by the Beadle team, however, supported the one gene—one enzyme hypothesis. They eventually identified mutations for all the growth factors, amino acids, and nucleic acids.

Beadle’s team now had a simple method of determining biochemical pathways. In a biochemical pathway,

explained Meyerowitz, one chemical is changed into another via a series of intermediates, and each change is catalyzed by an enzyme. For example, in the pathway A – B – C – D – E, chemical A becomes B as a result of enzyme W, then enzyme X converts B to C, enzyme Y converts C to D, and enzyme Z converts D to E. Beadle and Horowitz showed that if they mutated the gene coding for enzyme Y, for example, they would get two effects. First, the substances coming after this stage in the biochemical pathway would be absent, so there would be no D or E. Second, there would be an accumulation of C as its conversion to D was blocked. By looking at the amount of chemical precursors in the biochemical pathway, and knowing the final product from normal *N. crassa*, they could eventually block every step in the conversion process.

Not only did their research show that each gene was responsible for a protein that implemented a single enzymatic step in a biochemical pathway, but successive mutations could also be used

to determine the order of the steps. As Horowitz later wrote, this work was revolutionary. It bridged the gap between genetics and biochemistry and ushered in the age of molecular biology.

When Beadle left Stanford in 1946 to chair Caltech's biology division, Horowitz came with him as a research assistant, becoming an associate professor in 1947.

The one gene–one enzyme hypothesis was regarded as a vast over-simplification, said Werner Maas at the memorial service. Now professor of microbiology, emeritus, at the New York University School of Medicine, Maas was a colleague of Horowitz who also joined Caltech in 1946. He recalled how Max Delbrück had raised a very serious objection to the conclusions: perhaps their method had only found a small subset of genes that coded for one enzyme, and missed the much larger set that coded for many enzymes. In response, Horowitz came up with the ingenious solution of using temperature-sensitive mutants; these act like normal fungi (or bacteria) at one temperature,

but are mutants at another. With Urs Leupold, he isolated and tested temperature-sensitive mutants of both *N. crassa* and *Escherichia coli*, and found, to his immense relief, that the majority of mutants of both species was indeed the one gene–one enzyme type. Leupold and Horowitz presented the results at the 1951 Cold Spring Harbor symposium, after which the hypothesis was widely accepted. (Delbrück had by that time lost interest and was not at the symposium.) Horowitz later admitted to Maas that before he found a way to answer Delbrück's objection, he had felt quite desperate.

"It was a brilliant experiment," said Meyerowitz. "The history of conditional mutants—the condition in this case being temperature—after 1951 is enormous, and it's all due to a seed planted by Horowitz."

Beadle and Tatum were awarded the 1958 Nobel Prize in Physiology or Medicine for their work on how genes regulate chemical events (they shared it with Joshua Lederberg, who worked on bacterial genetics). In his Nobel speech at the award ceremony, Beadle gave much of the credit to Horowitz and his coworkers.

He also told the Stockholm audience about an important application of the one gene–one enzyme hypothesis that Horowitz had published in 1945, while still a postdoc. In this paper, he speculated on how biochemical pathways could have evolved from a succession of mutations. Horowitz suggested that, initially, the organism would have got the end product of the pathway, a chemical it needed, directly from its environment. At some point, a mutation in a gene produced an organism able to manufacture this end product itself from another chemical found in the environment. A subsequent mutation could then allow it

to biosynthesize that chemical as well, and so on until the whole pathway had evolved. Each successive mutation would produce a generation of organisms that were less dependant for survival on the availability of chemicals in their environment, conferring a big evolutionary advantage.

With this thought experiment, Horowitz inaugurated the study of evolution at the molecular level. "If the present-day proponents of intelligent design would go back 60 years and read this paper," said Meyerowitz, "I'm sure they'd drop the whole thing."

Horowitz was made a full professor in 1953. Despite a tempting offer from Delbrück to join his bacteriophage group, he stayed loyal to *Neurospora*, and when Beadle moved to Chicago in 1961, Horowitz elected to stay at Caltech. He served as executive officer for Caltech's Division of Biology from 1971 to 1976, and as chair from 1977 to 1980, before becoming a professor emeritus in 1982.

In 1965, he moved to JPL for five years to head the lab's bioscience section, which had been set up to plan for the biological exploration of Mars. To see what types of life forms could survive in the harsh Martian environment, he dispatched a team of microbiologists to Antarctica—the nearest analog on Earth. They found only a very small number of soil bacteria there, which didn't bode well for the chances of finding life on the Red Planet.

Between 1965 and 1970, Horowitz worked on the Mariner missions, and, with George Hobby and Jerry Hubbard, designed an experiment for the Viking mission that would test the Martian soil for signs of life. Once on the planet, their instrument would incubate a soil sample in carbon dioxide and carbon monoxide—some of which was radioactively tagged—in simulated Martian



Horowitz was caricatured by Swiss geneticist Hans Gloor when he was a visiting postdoc at Caltech between 1947 and 1948. Image courtesy of the Caltech Archives.

sunshine. After incubation, the soil would be analyzed in a simple pyrolytic gas chromatograph for the presence of organic compounds labeled with carbon-14. If the level of radioactive carbon exceeded a predetermined background level, it would show that there had been organic synthesis during incubation. The Viking craft, finally launched in 1976, landed at two sites, Chryse Planitia and Utopia. Although several samples were tested at both sites, all the results were negative, as were those for the other life-detection instruments on board. “Horowitz’s work was important in a negative way,” said Baltimore at the service. “He showed that life really couldn’t exist on the surface of Mars—but we’re still looking beneath the surface and hoping for the best.”

Returning to Caltech in 1970, Horowitz started to look for mutations that would enable *Neurospora* to live with less water. None were found, but his research led to the discovery of some interesting growth factors—chelating agents called siderophores that were involved with iron uptake. Out of this work grew the important realization that iron in our bodies has to be kept very closely “locked up” by proteins to stop harmful organisms from getting at it with their chelating agents.

In 1998, the Genetic Society of America awarded Horowitz its highest honor, the Thomas Hunt Morgan Medal. He was a member of the National Academy of Sciences and the American Academy of Arts and Sciences, and the holder of a NASA Public Service Medal.

But Horowitz was not concerned with gaining honors. “My father always felt that he had been incredibly lucky to have landed at the right place at the right time, which for him was Caltech at the dawn of the era of biochemical genetics,” said his daughter,

Elizabeth, at the memorial service. “He was very modest about his achievements and had absolute integrity in his approach to science, untainted by self interest or the desire for personal gain.” Son Joel talked about his father’s love of classical music and opera, and how he played the piano every evening and tended his roses. He also enjoyed hiking and camping in the mountains.

His great generosity to Caltech resulted in part in the George Beadle Professorship of Biology (Meyerowitz is the second holder of that chair) and the Norman Horowitz lecture series. After the death of his wife in 1985, he set up the Pearl S. Horowitz book fund in the biology division in her honor. According to Meyerowitz, he also left the Institute a very valuable gift in his will—his house in Altadena. The proceeds of the sale of the house will supplement the Horowitz lecture fund, with the balance used to assist graduate students in the Division of Biology.

In his 1986 book, *To Utopia and Back: The Search for Life in the Solar System*, Horowitz concluded: “The failure to find life on Mars was a disappointment, but it was also a revelation. We are alone, we and the other species, actually our relatives, with whom we share the earth. If the explorations of the solar system in our time bring home to us a realization of the uniqueness of our small planet and thereby increase our resolve to avoid self-destruction, they will have contributed more than just science to the human future.”

Horowitz was predeceased by two brothers who were also scientists, one a petroleum engineer, the other a chemist. He is survived by his daughter, Elizabeth; his son, Joel; and two grandchildren.

□—BE



Tom Apostol and Mamikon Mnatsakanian.

THREE MATH PAPERS . . .

Who says mathematicians do their best work before the age of 30? Eighty-two-year-old Tom Apostol, professor of mathematics, emeritus, and director of Project MATHEMATICS!, along with 63-year-old project assistant Mamikon Mnatsakanian, received this year’s Lester R. Ford Award of the Mathematical Association of America.

The award is for “an article of expository excellence” published in *The American Mathematical Monthly* or *Mathematics Magazine*, but in 2004, each of the three articles Apostol and Mamikon published was a worthy candidate, and the judges couldn’t decide

between them. They solved the dilemma by awarding the prize to all three papers—a first in the history of the Association.

The articles, entitled “Isoperimetric and Isoparametric Problems,” “A Fresh Look at the Method of Archimedes,” and “Figures Circumscribing Circles,” give classical geometry a modern twist and modern geometry a classical twist, said the citation, producing new and surprising results in areas that have been mined for centuries.

We featured some of this innovative work in *E&S*, No. 3, 2000. □—BE