NATIONAL ACADEMY OF SCIENCES

NORMAN HAROLD HOROWITZ
1915—2005

A Biographical Memoir by
RAY D. OWEN

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March 19, 1915–June 1, 2005

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NORMAN HOROWITZ (elected to the National Academy of Sciences in 1969) was distinguished for his accomplishments in two main fields. First, he early joined the program in biochemical genetics centering on work with Neurospora and became a leader in that area. He is credited with recognition and elaboration of the one gene-one enzyme hypothesis, providing insight into the primary nature of gene action. His 1945 paper is considered by many to be historically the definitive treatment of evolution at the level of molecular biology. Second, he later took up the subject of extraterrestrial exploration, and his 1986 book, To Utopia and Back, was a valued account of that experience. Along the way he taught and mentored students and lived a full life, including active interests in music and literature.

Born in the Squirrel Hill district of Pittsburgh, Pennsylvania, on March 19, 1915, Norman was the oldest of three brothers. His father had come from Austria about 1900; he owned and ran a small business. His mother was from Boston. The boys attended public schools and weekly a Reformed Jewish religious school. Norm, however, became skeptical about religion before his confirmation at age 16.[1] Much of his boyhood time was spent hiking in Frick's Woods near home, and in sports and games, including chess. He did well in school, and remembered especially the seventh-grade class in general science as well as fine teaching in mathematics and English, not in biology, chemistry, or physics. The other two valedictorians in his class were Philip Morrison, who like Norm later became a member of the National Academy of Sciences, and Jack McKee, a member of the National Academy of Engineering.

Attending the University of Pittsburgh on a scholarship to major in zoology, Norm was fortunate in his junior and senior years to be able to conduct independent research in Prof. H. H. Collins's laboratory. He followed histiologically the rejection of transplanted tissues in salamanders. The work was published in the *Proceedings of the Pennsylvania Academy of Sciences* when he graduated in 1936 and in the *Journal of Experimental Zoology* in 1937. He met Pearl Shykin, then a senior at Radcliffe majoring in biology, at Woods Hole in 1937. They were married in 1939, and had two children, Joel (b. 1941) and Elizabeth (b. 1945). Much of Norm's time and attention late in his life was devoted to Pearl's care during her long terminal illness; she died in 1985.

On the advice of his genetics teacher at Pitt, Prof. G. M. McKinley, Norm applied for graduate work in T. H. Morgan's decade-old biology department at Caltech. He was accepted and given a teaching fellowship. His paper on transplant rejection in salamanders was of interest to Morgan and others at Caltech, and played an important part in the decision to admit and support him. On his arrival as a new graduate student in 1936 Norm says he went to Morgan's office. Morgan looked at him over the edge of his spectacles and told him he was to work with Albert Tyler.[1] Tyler, Caltech's first Ph.D. in biology, shared Morgan's interests in invertebrate development. Norm as a graduate student enjoyed intervals at the marine laboratory in Corona del Mar and at Woods Hole in company with Tyler and Morgan. Seven papers were published jointly by Tyler and Horowitz in 1937 and 1938. Norm became sole author in 1939 and 1940 of four more, on aspects of the respiratory metabolism of the marine worm *Urechis.*

Receiving a National Research Council Postdoctoral Fellowship recommended by Morgan, Norm would ordinarily in those days have gone abroad for postdoctoral training. But the war was in progress, and he chose to work with Stanford's Douglas Whittaker, distinguished mainly for his studies of the developmental biology of marine organisms. After that year, Norm returned to Caltech to work for two years with biochemist Henry Borsook on calcification in bone formation, a subject of interest in military medicine, which made him draft exempt.

In 1941 George Beadle visited Caltech to give his historic seminar on *Neurospora* biochemical genetics. Norm had become acquainted with Beadle at Stanford; Beadle at the time was working with transplantation of imaginal discs in *Drosophila* larvae. Both were pleased to have him return to Stanford to work with the new system in *Neurospora.* "The next four years," Norm wrote, "were scientifically the most exciting of my life."[1]

The key concept developed by Beadle and Tatum at Stanford made use of the fact that cultures of wild-type *Neurospora crassa* could grow well on a minimal medium containing only certain inorganic salts, a suitable carbohydrate such as sucrose, and the vitamin biotin. Mutant *Neurospora* often lost that ability but would grow on much richer media. Adding particular components to the minimal medium narrowed the requirements for growth of particular mutants; it could be shown that a mutant missing a biochemical ability could be matched with mutation in a gene. Norm, with his expertise in both biochemistry and genetics, fitted well into the Beadle-Tatum program. Among his several contributions were his definition with Beadle of a method for determination of choline by use of a mutant of *Neurospora* (1943), and with Adrian Srb the genetic control of the ornithine cycle (1944). It was evident that genes affected biochemical processes by controlling enzymes, and Norm became especially interested in d-amino oxidase.

In 1945 Beadle had put forward the hypothesis that each gene controlled the production of a particular enzyme, and that each enzyme was controlled by a particular gene—the one gene-one enzyme hypothesis. Horowitz became a major proponent of the hypothesis, to the extent that he regarded doubters as hostile. One of his reactions to doubt was to a comment by Max Delbrück, who expressed a thought that the procedures in the *Neurospora* program might be selective for specific examples of the hypothesis, and that other relationships could be more complex. "It occurred to me," Norman wrote later,[1] "that this contention could be tested by the use of temperature-sensitive mutants, of which we had turned up a couple of dozen in the course of the mutant hunt." In 1951 with Urs Leopold, a research fellow working in his lab, the study was extended to *Escherichia coli,* with isolation of 161 biochemical mutants that had lost the ability to grow on minimal medium at 40°C, but were still able to do so at 25°C. Only 23 percent of these mutants had requirements not satisfied by the complete medium. These observations indicated that the selective effect of the complete medium in the standard procedure in eliminating the recovery of multifunctional genes must be small. The results favored the one gene-one enzyme theory.

Of course, later work at the molecular level by others found numerous important exceptions to a one-to-one quantitative relationship between genes and biochemically active products. Hemoglobin was an early example; at first it could be seen to depend not on one but on two independent loci.

The apparent contradiction was resolved when it was found that hemoglobin is a tetramer made up of two polypeptide chains, each under the control of a specific gene. In the other direction, examples of more than one enzyme being affected by a particular gene included, for instance, alternative splicing producing different products from a single genetic region. Nevertheless, the early generalization—one gene-one enzyme—greatly influenced thought of how genes affected inherent functions. It implied that "the gene transferred functional specificity, and therefore structural information, to its cognate protein."[1] As a side effect, the use of temperature-sensitive mutants became a standard procedure in microbial genetics.

On the Caltech faculty Norm pursued active studies in biochemical genetics for 20 years, and served as an excellent teacher, mentor, and campus citizen in every regard. But in the late 1950s he became primarily interested in the space program, especially at the Jet Propulsion Laboratory (operated for NASA by Caltech), the lead center for planetary exploration. During 1965-1970, he served as chief of the biosciences section at JPL, with major emphasis on Martian biological exploration. He remained on the Caltech faculty while discharging responsibilities at JPL, and returned to full-time on the campus in 1970. He continued to produce papers on the Viking landings on Mars, culminating in his book *To Utopia and Back* (1986). The book is in part the expected account of looking for life on Mars: "How we did it, what we found." But it greatly surpasses that expectation and reflects the breadth, depth, care, and character of Norm's more general scholarship. It begins with a concise chapter on "What Is Life," concluding that our concept of "life" must be broad enough to let us recognize it in any guise, and precise enough to prevent our finding it where it does not exist. He delves into an incisive discussion of life and the genetic mechanism and proceeds to a concise outline of life and carbon chemistry. He then devotes a chapter to spontaneous generation and panspermia, concluding as an article of his scientific faith that "through all space and all time, life proceeds from life and from nothing but life. How, then, did life originate on the Earth?"

The question leads to Chapter 3: "The Origin of Life: Chemical Evolution," introduced with a quotation from Theodore Roethke's *The Longing*: "Out of these nothings—All beginnings come." Given the principles established in the first two chapters, the author could then turn to the subject of life on other planets, detailing the failure by the Viking landers to find life on Mars. He concludes introspectively,

> The failure to find life on Mars was a disappointment, but it was also a revelation. Since Mars offered by far the most promising habitat for extraterrestrial life in the solar system, it is now virtually certain that the earth is the only life-bearing planet in our region of the galaxy. We have awakened from a dream. We are alone, we and 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.

Here again, Norm was sensitive to doubts of his conclusions, and his last substantial scientific contribution (1988) was a considered reply to such doubts. He continued to produce reminiscent notes until near his death in 2005. I had the pleasure of interviewing him for the "Conversations in Genetics" project of the Genetics Society of America.[3] (Norm had been elected president of the society and had received its Morgan Medal in 1988.) Part of our memory of him recurs annually at Caltech in the endowed Horowitz lecture.

His death in 2005 elicited a number of admiring testimonials and obituaries. Perhaps the most thoughtful are one by Ivan Oransky in *Lancet*[2] and one by Robert L. Metzenberg in *Genetics*.[3] Incidentally, Eric Selker's *Perspective on Metzenberg*[4] quotes a tribute by Metzenberg to Horowitz, "Somehow, Norm always managed to tell the truth without becoming a scold. There can never be enough of such people, and his legacy must be kept alive."

NOTES

1.From a manuscript copy of Horowitz's autobiographical sketch submitted to the National Academy of Sciences in 1988.
2. I. Oransky. Obituary: Norman Horowitz. *Lancet* 366(2005):116.
3. R. L. Metzenberg. Norman Harold Horowitz, 1915-2005. *Genetics* 171(2006):1445-1448.
4. E. U. Selker. Robert L. Metzenberg. June 11, 1930-July 15, 2007. *Genetics* 178(2008):611-619.

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