Leonard S. Lerman

1925–2012

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Tom Maniatis
and Sidney Altman

NATIONAL ACADEMY OF SCIENCES

LEONARD SOLOMON **LERMAN**

June 27, 1925–September 19, 2012

Elected to the NAS, 1986

Photo courtesy of the family of Leonard S. Lerman.

By Tom Maniatis and Sidney Altman

Leonard S. Lerman (Elected to the NAS in 1986) was a brilliant and creative molecular biologist who throughout his life generated novel ideas and scientific approaches to the study of DNA.

Leonard was born in Pittsburgh, Pennsylvania, to Meyer and Freamah Lerman, who had immigrated to the United States from the Ukraine. Freamah had come directly to Pittsburgh and Meyer moved to Pittsburgh from New York when his leftist political views became unpopular there.

From early childhood, Leonard demonstrated an unusual level of curiosity about science. Although neither of his parents had attended college, their encouragement led him and his younger brother, Omar Khayyam Lerman, to excel. As a child, Leonard's enthusiasm for science extended beyond his chemistry set, as he used his allowance to obtain supplementary chemicals necessary for experiments not found in the set's guidebook—an early sign of his creativity. His father purchased the chemicals during frequent business trips.

Leonard attended Allderdice High School in Pittsburgh, where an extraordinary chemistry teacher, Lon Colburn, further inspired his interest in science. At the age of 16, Leonard won a science contest on a Pittsburgh radio show, with the prize being a scholarship to the Carnegie Institute of Technology (now Carnegie Mellon University), where he completed a B.S. in chemistry in only five semesters. At that time the United States was engaged in World War II, and Lerman joined the Explosives Research Laboratory in Bruceton, PA, where he designed and tested explosives—a remarkable position for such a young person right out of college. When later asked if this was not highly dangerous work, Lerman replied, "Yes, but I was very VERY careful." Indeed, in his home laboratory Lerman had already developed the meticulous habits that were to characterize all of his subsequent research.

After the war, Lerman entered graduate school in chemistry at the California Institute of Technology, where he worked in the laboratory of Linus Pauling, who had become interested in antibody specificity. In his thesis research, Lerman made the significant discovery, independently from others, that immunoglobulin G antibodies are bivalent (1). Awarded his Ph.D. in 1950, Lerman subsequently did postdoctoral work with Leo Szilard at the University of Chicago, one of the centers of the nascent discipline of molecular biology. This field, emerging in the late 1940s and early '50s, was driven by physicists and chemists who, like Szilard, had become interested in biology. A brilliant and imaginative physicist, Szilard had conceived of the possibility of a nuclear chain reaction. Concerned that the Germans might develop an atomic bomb, he drafted a letter to President Franklin D. Roosevelt, signed by Albert Einstein, which led to the establishment of the Manhattan Project. During this postdoctoral period, Lerman developed the method of affinity chromatography, which he used for the purification of an enzyme and to purify and subdivide a population of heterogeneous antibodies (2–4).

Lerman's lab and home in Denver became a way station for molecular biologists— for example, ex-physicist Francis Crick—making cross-country tours.

Leonard, front, with parents Meyer and Freamah and brother Omar, approximately 1930. (Photo courtesy of the family of Leonard S. Lerman.)

In 1953 Lerman became an assistant professor in the Department of Biophysics at the University of Colorado's School of Medicine in Denver. The department was led by Theodore Puck, a chemist who also had migrated to biology and became a pioneer in the field of somatic cell genetics. Lerman's lab and home in Denver became a way station for molecular biologists—for example, ex-physicist Francis Crick—making crosscountry tours. Crick and his close colleague, Sydney Brenner, would later interact with Lerman during his sabbatical leave at the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, England.

Leonard, right, with Theodore Puck at the University of Colorado Medical School, mid-1950s. (Photo courtesy of the family of Leonard S. Lerman.)

On a visit to New York, during his time in Denver, Lerman looked up Maurice Fox, a former colleague from Szilard's laboratory, who was then in the laboratory of Rollin Hotchkiss at the Rockefeller Institute. At this time, the possible role of DNA in the genetic transformation of bacteria was being hotly debated; and Lerman and Fox had lengthy discussions regarding experiments to investigate the possible mechanism of such a transformation. Lerman (with Leonard Tolmach) and Fox proceeded independently to carry out their jointly conceived plan, relying on radioactively labeled (32P) DNA to follow incorporation of DNA into bacterial cells—among the first uses of labeled DNA for such a purpose. The results provided quantitative information on the stoichiometry of the transformation event, showing that incorporation of the tracer into recipient cells was concomitant with genetic modification (5, 6).

Through ingenious use of a battery of physical measurements, Lerman demonstrated that acridines bind to DNA by inserting themselves between adjacent stacked base pairs— a process he named "intercalation"—which results in the partial unwinding of the DNA double helix and an increase in viscosity.

Beginning in 1957, Lerman participated in a series of meetings on DNA-mediated transformation at the Wind River Ranch in Wyoming. Other attendees included Fox, Sol Goodgal, and Julius Marmur. Lerman organized the third meeting, which was memorable not only for the presence of Francis Crick and Sterling Emerson but also because it became necessary to place an SOS call to Denver for someone to bring a slide projector and screen.

In the late 1950s, while engaged in his studies on genetic transformation in bacteria, Lerman began to think about the structure of complexes of DNA with polycyclic aromatic compounds such as acridines, which were known to induce mutations in bacteriophages. Through ingenious use of a battery of physical measurements, Lerman demonstrated that acridines bind to DNA by

inserting between adjacent stacked base pairs—a process he named "intercalation"—which results in the partial unwinding of the DNA double helix and an increase in viscosity (7–10). The results are relevant to the action mechanisms of certain antibiotics, antiparasitics (including antimalarials), anticancer agents, and carcinogens and mutagens. In addition, understanding the mechanism of DNA binding by acridines was later instrumental to studies by others, including James Wang and Jerome Vinograd, in DNA supercoiling, nucleosome-DNA interactions, the mechanism of DNA unwinding by topoisomerases, and the use of intercalating dyes in DNA detection by ethidium bromide.

Some of Lerman's work on intercalation was carried out in 1959 and 1960 while he was on sabbatical leave at the MRC Laboratory of Molecular Biology in Cambridge. At this time, Crick and Brenner were using acridine mutagenesis of T4 bacteriophage to study the nature of the genetic code. Lerman's analysis of intercalated DNA provided a physical basis for the inference, from genetic analysis, that the acridine-induced mutations were insertions and deletions that lead to frame shifts in the genetic code (11). These mutations were critical for the hypothesis, formulated by the Crick-Brenner group, that the genetic code consists of three nucleotides encoding a single amino acid (12). Thus Lerman's findings, and his timely presence at the MRC, contributed to one of the classic papers in molecular biology.

In 1965, Lerman moved to Vanderbilt University in Nashville, TN, where he initiated studies on transitions in individual DNA molecules from an extended structure to a highly compact structure, similar to that of DNA packaged in bacteriophage heads or condensed chromatin. This structural transition was induced by high concentrations of polyethylene glycol and salt. Wide-angle X-ray scattering studies of the compact DNA led to the conclusion that the higher-order structural transition occurs without a dramatic alteration of the secondary DNA structure, presaging the same conclusion for the structure of compact DNA in chromatin (13, 14).

Throughout Lerman's career his command not only of chemistry but also of physics was applied to rigorous studies of DNA structure. An example was his next contribution—denaturing gradient gel electrophoresis—which he developed after moving, in 1976, to the Department of Biological Sciences in the State University of New York at Albany. Lerman used his knowledge of the movement of rigid double-stranded DNA fragments through a polyacrylamide gel matrix, as well as of the effect of partially denatured DNA on mobility, to separate DNA fragments of identical length but different base compo-

sition and to identify point mutations in DNA. He designed and built an apparatus in which a temperature gradient is precisely generated across such a gel. As individual DNA fragments move through the gel, the lowest- temperature melting region of each DNA fragment melts partially, creating a denaturation "bubble," which results in an abrupt decrease in mobility of that fragment (15, 16). Based on the sequence of the DNA fragment, Lerman calculated precisely where, in the temperature gradient, the transition in mobility would occur; and he was able to predict that normal and mutant fragments with single nucleotide differences could be separated in the gel system.

Leonard, left, with his brother Omar in 2009. (Photo by Lisa Steiner.)

Leonard in his home workshop, 2008. (Photo by Lisa Steiner.).

Remarkably, the mathematically derived prediction proved to be correct (17). Further modification of the method made it possible to detect single base mutations in total human genomic DNA (18–20). Lerman's denaturing gradient gel electrophoresis method was also used to develop a method for saturation mutagenesis of regulatory DNA sequences (21), and to carry out the first single nucelotide saturation mutagenesis study of a eukaryotic promoter (22). Despite the revolution in DNA sequencing, denaturing gradient gel electrophoresis remains a useful low-cost tool for detecting mutations in individuals with genetic diseases and for microbial ecology (20). To date there are over 7700 citations to "denaturing gradient gel electrophoresis" or "dgge" in the literature and the number appears to be increasing; in the year 2000 there were 206; in 2005, 430; and in 2012, 789.

In 1984 Lerman left Albany to lead a DNA diagnostics program at the Genetics Institute in Cambridge, MA, an early biotechnology company. Fox, then chairman of biology at the Massachusetts Institute of Technology, subsequently invited him to move to MIT

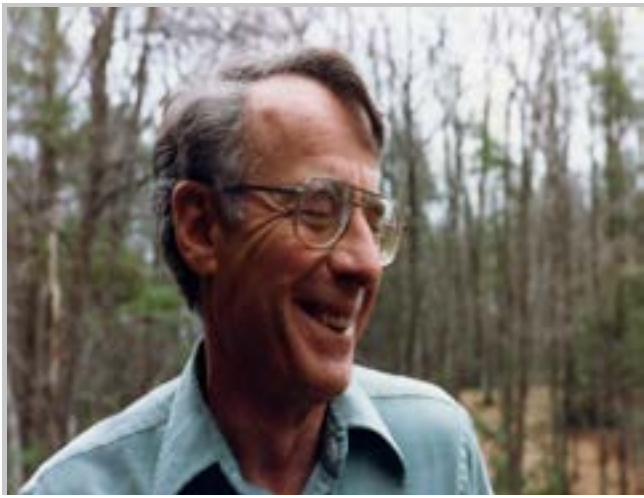
Leonard on Schroon lake, Adirondacks, New York State, 1996.
(Photo courtesy of the family of Leonard S. Lerman.)

where, in 1987, Lerman assumed the position of senior lecturer and built a small research group.

Later, as Lerman's health deteriorated, he was developing the idea of a pressure-dependent, rather than temperature-dependent, DNA polymerase chain reaction; and he was building a prototype device along those lines in collaboration with Ian Hunter (of MIT's mechanical engineering department). Such efforts were examples of Lerman's originality and his talent as a gadgeteer, which he repeatedly demonstrated throughout his life. In fact, long before its popular introduction by others, Lerman developed a hand-held TV remote-control device for turning off the sound during commercials. His family and friends used it for years before such gadgets became ubiquitous. In his laboratory, Lerman designed and built nearly all of the electronic equipment —from power supplies to pump control systems to gradient makers—used in his experiments. On most Saturday mornings he could be found in his elaborately equipped home workshop designing and building a new instrument.

Lerman was an excellent advisor and mentor. Both authors recall that he demanded rigorous and independent thinking, and a thorough grasp of scientific principles. In some ways, his method of teaching was Socratic, as the questions we asked were usually answered by another question, which probed our depth of understanding and thinking. A discussion of how we might attack the problem at hand would follow, usually leading to his comment that "You decide!" While this approach could sometimes lead to despair, on many occasions it resulted in the conception of an independent study, a new direction, or the design of a new gadget or technique directed toward solving the problem. We believe that Lerman's mentoring method was invaluable in developing our problem-solving abilities and in our subsequent efforts to establish independent research programs.

The atmosphere in Lerman's laboratory was congenial and stimulating. Both of us benefited from the presence of Rose Litman, who for many years was an independent investigator associated with Lerman's group. Like Leonard, Rose demanded rigorous thinking, and she was a thoughtful advisor and mentor. She was also an excellent teacher and served as the senior associate in a group that had many visitors from different nations as a consequence of Lerman's extensive international connections. Lerman and Litman made it seem as if the world was open to everyone in the group, and we profited from those connections.



Leonard in Alaska, 1995.
(Photograph by Averil Lerman.)

Lerman's first marriage to Claire Lindegren in 1952 ended in divorce in 1973. His second marriage, to Elizabeth Knox Taylor, also ended in divorce. In addition to Lisa Steiner, his partner and close companion for 20 years, he is survived by three children from his first marriage—Averil, Lisa, and Alexander—and seven grandchildren. Lerman died at his home in Cambridge, MA, on September 19, 2012, after a long illness.

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