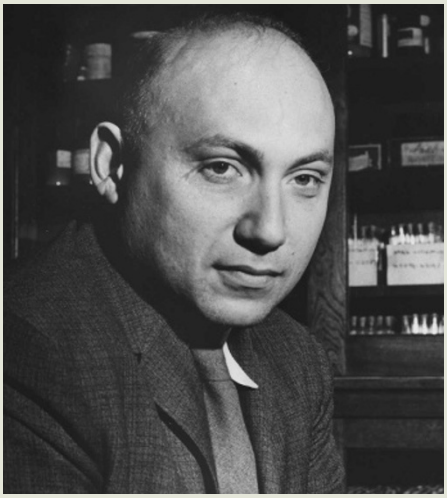
OBITUARY

Joshua Lederberg (1925–2008)

Decisive discoveries in bacterial genetics.



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I think it was 1941 when I first met Josh Lederberg. The location was the American Institute Science Laboratory in New York city, in the shadow of the Empire State Building. These labs were established to enable high-school students to conduct after-school research, and were an inspiring place for the science nerds of the time. Lederberg and I had much in common. We were born in the same year, spent much of our youthful spare time in branches of the New York Public Library, and were prompted to enter medical research by reading Paul de Kruif's *Microbe Hunters*.

Even then, his talent and energy marked him out. Lederberg, who died on 2 February 2008, became a brilliant biologist and an exceptional leader whose influence extended to space science and computing.

He was educated at Stuyvesant High School, an élite institution that produced four Nobel laureates in science, and then Columbia University. But before completing his medical education at Columbia he migrated to Yale University to do research. Inspired by Oswald Avery's discovery that DNA, not protein, is the genetic material in *Pneumococcus*, he embarked on testing the widely held hypothesis that bacteria simply divide into two offspring from a single genome. Lederberg, however, showed that sexual reproduction occurs in *Escherichia coli*, so revealing both an unexpected feature of microbial reproduction and providing an essential tool for genetic research and biotechnology.

More was to come following the award of his PhD in 1947 and a move in that same year to the University of Wisconsin, Madison. Together with colleagues, including Esther Zimmer (to whom he was then married) and Norton Zinder, he discovered that viruses that infect bacteria can transfer genetic information between their hosts. This mechanism — transduction — was an unexpected way of altering the host's genetic make-up, and later assumed special significance with the recognition that viral sequences can be inserted in the human genome and can presumably be inherited. The discovery of transduction opened a vast area for research on the role of viruses in evolution and disease, and — even more intriguing — into the non-pathological characteristics of microorganisms.

Another surprise was the finding that small, ring-shaped pieces of DNA, termed plasmids, reside in microbial cells and are distinct from chromosomal DNA, being capable of autonomous replication. Plasmids can be introduced into other cells to produce vast amounts of useful proteins such as human insulin and the hepatitis B virus vaccine. Lederberg's work was seminal in initiating a new approach to biology based on the genome and its interactions with the environment. This was recognized by the award of the Nobel prize in 1958, at the age of 33, which he shared with George Beadle and Edward Tatum.

By then he was already widening his horizons, stimulated in particular by the launch of Sputnik on 4 October 1957. He was excited by the prospect of space exploration, but was also concerned about possible biological cross-contamination between Earth and other planetary bodies. In December 1957 he wrote to the US National Academy of Sciences (NAS) to warn of this danger. The eventual consequence was that objects and crews returning from Moon missions were subject to decontamination and quarantine.

Lederberg was appointed as a founder member of the NAS Space Science Board in 1958, and continued to stimulate both professional and public interest in biological space research (particularly in his "Science and Man" columns in *The Washington Post*). He coined the word 'exobiology', which signalled the arrival of the discipline dedicated to the search for extraterrestrial life. This term was criticized as inappropriate, because there was no life known beyond Earth, and as designating a discipline without a subject. Its descendant discipline is 'astrobiology', a term often used interchangeably with exobiology. Astrobiology involves study of the origins of life on Earth, and testing the hypothesis that life exists elsewhere, maintaining Lederberg's vision of biology as an essential component of space research.

His connection with space science became especially close when he was involved in planning, along with colleagues, experiments to be carried by the Viking landers to seek evidence of microbial life on Mars. The experiments consisted of the collection and spectrometric analysis of soil samples, and the landers commenced operations in 1976. The results were inconclusive, but they marked the beginning of a search that continues in the astrobiology programmes in the United States and elsewhere.

Stimulated by his space research, Lederberg became a pioneer in the use of computers for biology and medical science. The DENDRAL program aided the determination of chemical structures from the spectrometric data collected on the Viking mission. Later, it was used to characterize structures of other compounds and was eventually applied to the organization and analysis of large biomedical data sets. This in turn led to medical 'expert systems', including INTERNIST, an expert system for clinical diagnosis and treatment.

As if all of this were not enough, Lederberg took on senior management responsibilities at Stanford University, to which he moved in 1959, and other institutions, culminating in his appointment in 1978 as president of the Rockefeller University in New York. He served on various prominent committees and agencies, and was an adviser to many US presidential administrations. He was concerned about the hazards of biological warfare and was a consultant to the US Arms Control and Disarmament Agency, and served on the Defense Science Board, which advises the Department of Defense. He was also a member of the science advisory board of the NASA Astrobiology Institute, an intellectual offspring of his early interests in space biology. In 2006 he was awarded the US Presidential Medal of Freedom.

As a researcher, Lederberg emphasized the importance of honesty and clarity in reporting scientific results. He recognized that science is a powerful problem-solving tool but that it has its limitations for individuals and society. His father was a rabbi and may have wanted his son to follow in his footsteps, which perhaps prompted Josh's awareness that acquiring knowledge is a blessing, yet comes laden with obligations.

Scientists are not usually thought of as heroes. I write as an old friend and colleague, but to my mind Joshua Lederberg was just such a man. Through his far-ranging interests and achievements, often accomplished against entrenched opinions, he has left an enduring imprint on science.

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