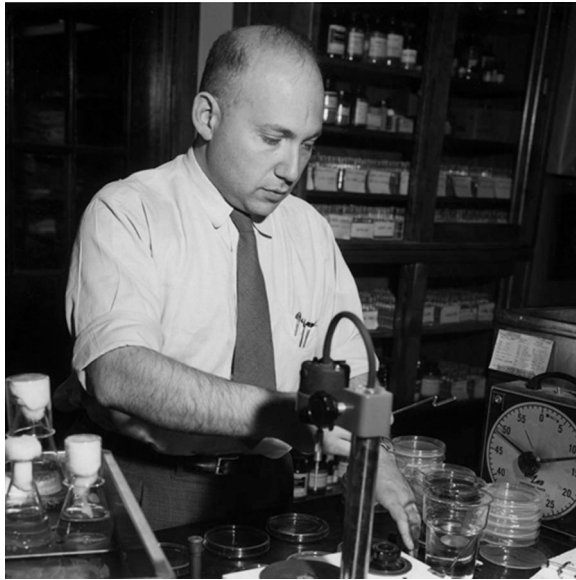
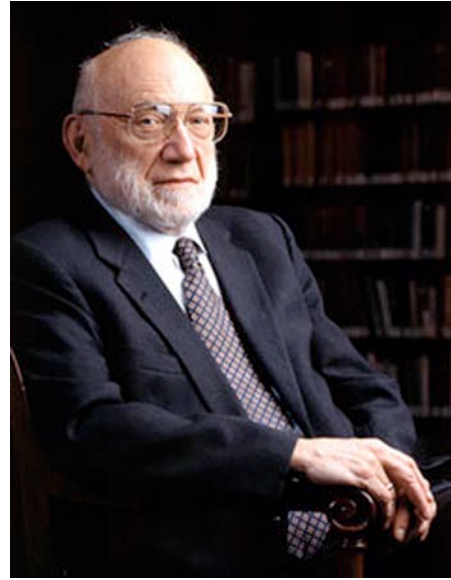


## Science as Oath and Testimony: Joshua Lederberg (1925–2008)



Joshua Lederberg, Wisconsin 1958 (courtesy National Library of Medicine).



Joshua Lederberg, New York 2003 (courtesy Rockefeller University).

*The demand for the meticulous prediction of which experiments will be done tomorrow, the detailed protocol of grant applications . . . flies in the face of scientific discovery, which is full of false starts, the serendipity, the unpredictability of any great discovery or any real important consequence.*

Joshua Lederberg, Stanford, 1978 (1)

*Publication . . . converts private to public knowledge, in the service of registering a private claim of original authorship—in science, of discovery. Above all, the act of publication is an inscription under oath, a testimony.*

Joshua Lederberg, Marine Biological Laboratory, 1991 (2)

### STARTLED AND PRIVILEGED

Josh Lederberg was already worried a generation ago: “One of the major trends of scientific writings for the past century is the systematic falsification of the actual techniques and method of discovery (1).” Lederberg wasn’t concerned that published papers fail to mention the false starts, wrong turns, or dead ends on the road to discovery. He accepted the conventional forms of scientific publication, which he called “recipes for replication of the results.” He even praised the traditional format of the standard research report for its “pedagogical elegance” that prevented dragging in “all the dirty linen that led to the very fine fabrics that are eventually produced.” What troubled Lederberg most,

however, was that when we falsify the process of discovery we lead the gate-keepers of science astray. All of us are guilty, he argued, of persuading funding agencies to expect grant proposals neatly packaged as “recipes for replication” with no wiggle room for risk and innovation. He warned that government or private entities that required tidy recipes for proposed experiments would be “selecting against creativity” in research (1).

Joshua Lederberg used the evolutionary term “selection” accurately and with intent. The discussion took place at a 1978 Stanford symposium honoring the centenary of Claude Bernard’s death; it was co-sponsored by the French consul in San Francisco and took place at the Moët estate in the wine country. As expected, talk flowed as freely as vintage and soon the discussion turned to whether Bernard had learned anything from Darwin. A colleague suggested that a true scientific discovery is like a mutation, a quantum shift with selective advantage. To extend the analogy, Lederberg was asked whether system (pure theory) or experiment (the lab observation) was the best mutagen. His answer: Both. He was convinced that the “tension between system and experiment” directs the sort of sea change in science that Thomas Kuhn was to call a paradigm shift (3).

Joshua Lederberg’s own career illustrates the point. Discussing his own paradigm shift in a joint interview with Thomas Kuhn, he attributed it to a mixture of system and experiment:

*I was startled—and privileged—at age 21 to have made a surprising discovery that involved merging bacteriology and genetics. That was contrary to the wisdom of the time, which held that bacteria could not be crossed since they had no genetics. I've been puzzling about that ever since, because I felt the discovery should have been made 20 years before I was born (4).*

Perhaps the discovery could have been made in 1905, but not in the United States, and not by someone from Joshua Lederberg's background.

## THE IMPEDIMENTS OF PERSONALITY AND RACE

In the half century between Victory in Europe and the Mess in Mesopotamia, American biomedical science underwent a radical social transformation. Before World War II this country had made a respectable showing in science on the world stage, but we did not attain a pre-eminent role until real and perceived national needs (*i.e.*, the Hitler War, the Cold War, Star Wars, Bio terror) made resources available to pursue basic science in pursuit of practical goals. Programs such as the Navy's V-12 plan, the G.I. Bill, the establishment of the NIH, the "War on Cancer," the Apollo program, etc., made jobs, money, and facilities available countrywide for a generation of native and émigré scientists. Perhaps the best and the brightest of that generation was Joshua Lederberg; his three-fold achievements as scientist, public citizen, and communicator made him its spokesman.

Son of a rabbi, Joshua Lederberg attended Stuyvesant High School in Manhattan, one of the elite institutions established by Mayor Fiorella Laguardia to help sons and daughters of immigrants compete with graduates of posh private schools for admission to selective colleges. He entered Columbia College at the onset of the war in 1941 and enlisted in the Naval V-12 program (5). The Navy plan condensed premedical and medical studies into five or six years with the aim of producing Naval officers in quantity. In his sophomore year he began working part time in the laboratory of Francis J. Ryan on *Neurospora* while fulfilling his naval duties by working in a clinical lab at St. Alban's Naval Hospital. In June of 1946, Lederberg produced a respectable, if not astounding paper on back-crosses of *Neurospora* mutants with "Frannie" as first author (6).

That same year, and before completing his medical education at Columbia, he moved to Yale to work with Ed Tatum, who had been Ryan's mentor. This callow Columbia pre-doc published an astonishing and prescient paper that attracted as little attention at the time as Mendel's work on *Pisum sativum*. His single-authored letter in *Science* carried the presumptuous title of "A Nutritional Concept of Cancer (7)." Based on the example of *Neurospora* adaptation to selective nutritional media, he made the daring suggestion that human cancer is due to somatic mutation:

*The Neurospora experiments suggest a mutational origin [of nutritional adaptation] and that virus infection could play a corresponding role. A consequence of this*

*simple concept is that cancer cells may be found to differ in their growth factor requirements from cells of normal origin when grown in vitro (7).*

The passage anticipates not only the somatic mutation theory of oncogenesis, but also the possibility of directed mutation (*i.e.*, by a virus). Lederberg did not go on to address the problem of human cancer at Yale. He was excited by the finding in 1944 by Oswald Avery, Maclyn McCarty, and Colin MacLeod that DNA, and not protein, was the transforming principle in *Pneumococcus* (8) and moved from *Neurospora* to more tractable *E. coli*. He reasoned that if genes were made of pure DNA that could pass from microbe to microbe, then perhaps bacterial inheritance could follow Mendelian laws. Two centuries earlier, Linnaeus had shown sexual reproduction in plants—why couldn't this happen in bacteria? In Tatum's lab at Yale, Lederberg studied nutritionally adapted strains of K 12 *E. coli*—a lucky shot—and the results came fast. By June of 1947, they reported the discovery that led them to a podium in Stockholm a decade later:

*The conception that bacteria have no sexual mode of reproduction is widely entertained. This paper will be devoted to the presentation of evidence for the occurrence in a bacterium of a process of gene recombination, from which the existence of a sexual stage may be inferred (9).*

Lederberg and Tatum had tested the common wisdom that bacterial reproduction was by clonal division and found it wanting.

On the basis of this and related work, Lederberg was awarded a Yale Ph.D. in 1947 and was then faced with the problem of finding a job in academia. No luck at Yale or Columbia. Looking back, Lederberg recalled the obstacles of the day to an academic appointment of "a brash New Yorker, and a Hebraic one at that." Tatum wrote a number of letters of recommendation for young Josh to universities great and small "Tatum took pains to argue that my research qualifications far outweighed the impediments of . . . personality and race (10)."

## PLASMIDS IN MADISON

Eventually Lederberg received a job offer from the University of Wisconsin, Madison, for an assistant professorship of genetics. Internal records of the time show a faculty divided over the offer: "Lederberg's background was metropolitan [and] weeks passed before a consensus was reached with reference to inviting Lederberg to Wisconsin (11)." One might note that in the immediate postwar period, most Middle Western and a few Southern universities were far more hospitable to people of a "metropolitan" background than schools such as Yale or Columbia: the names of Salvador Luria, Max Delbrück, Rita Levi-Montalcini, Sol Spiegelman, and Henry Mahler come to mind. So, westward the course of Joshua.

For a dozen years, Lederberg flourished in the productive research environment of Madison: they were to be his golden years of discovery. Indeed, of his most cited papers, 9 of 10 date from the Madison years.

With co-workers that included his first wife, Esther Zimmer, he described lysogeny and lambda phage. They also found that small circular runs of DNA, which he called plasmids, are distinct from chromosomal DNA, and can undergo autonomous replication (12). He devised novel techniques in bacterial genetics used the world over, made the beta-galactosidase of *E.coli* a fit subject for analysis, and introduced penicillin as a means of selecting protoplasts. In 1952, with his student and life-long friend Norton Zinder, he uncovered a third mode of gene transfer in bacteria (13). The first, of course, was transformation (Avery, Mc Carty, and MacLeod), the second was bacterial mating which he and Tatum had discovered (9), and third was the viral transduction of Zinder and Lederberg, which they called “transduction.” The discovery of transduction (13) fulfilled his prophecy in the 1946 *Science* paper: viral sequences can be inserted at will into foreign genomes to produce heritable change. Transduction and plasmid exchange have become the basis of modern biotechnology.

The Madison era was capped by the Nobel Prize in 1958, when at the age of 33, he shared the laurels with Edward Tatum and George Beadle. His banquet speech reflects his lifelong personal modesty: “Pride is humbled as humility is exalted in the dignity and splendor of this occasion (14).”

## CITIZEN OF THE COSMOS

At the height of this research flurry, Lederberg turned his attention to protecting the planets. He had already been active on number of government advisory panels and commissions, but the intersection of space and microbiology presented him with a new career. The Russians had launched the satellite Sputnik in October of 1957 and Lederberg immediately understood that the microbes of earth and the heavenly bodies might cross-contaminate each other. Elected to the US Academy of Sciences in the spring 1957, he wrote a letter to the Academy in December warning them of this potential problem. Its solution required establishing a new field of study and novel research: the field acquired a new name, which Lederberg dubbed “exobiology” and its study has funded basic science for half a century. It was also due to his service on NASA and Academy committees on space biology, that manned and unmanned missions were quarantined and decontaminated at each end of the flight: he became a founder member of NASA’s space science board in 1958 (5).

In 1959, the young Nobel laureate moved to the sparkling new campus at Stanford’s School of Medicine, where he became the first chair of the Department of Medical Genetics. The medical school soon learned that microbiology and human genetics were part and parcel of the same universe. Josh went Haldane one better in his approach to the host/parasite issue:

*Haldane’s most pungent remark was, “It is much easier for a mouse to get a set of genes which enable it to resist Bacillus typhimurium than a set which enable it to resist cats.” That may well be; he overlooks the unmatched*

*evolutionary potential of the bacilli, which guarantees this will be an unending contest (15).*

While his bench research moved on apace, he turned his attention to information technology with the establishment of the Instrumentation Research Laboratory. In 1964, together with computer scientist Ed Feigenbaum and polymorphic Carl Djerassi, Lederberg developed Dendritic Algorithm (DENDRAL), an artificial intelligence system that sought to introduce inductive reasoning into chemical analysis. He was also responsible for Stanford University Medical Experimental Computer for Artificial Intelligence in Medicine (SUMEX-AIM) a nationwide time-share computer network for collaborative genomic and other biochemical research projects. These efforts brought together experts in widely different fields: social scientists with physicians, biochemists with computer mavens, engineers with astronauts, soil scientists with rocketeers. And when in 1976 the first Viking spacecraft sampled the soil of Mars, the instruments used for chemical analyses were those of Lederberg’s Instrumentation Lab (5).

Public service brought Lederberg frequently to Washington: he served on President Kennedy’s Panel on Mental Retardation, and was chairman of President Carter’s Cancer Panel. He consulted for the US Arms Control and Disarmament Agency during negotiations for the Biological Weapons Convention in Geneva. And from 1966 to 1971, he published a weekly column “Science and Man” in the *Washington Post* which addressed problems that ranged from germ warfare to civil liberty, from the Middle East to the middle of the earth. They were “metropolitan” in outlook: liberal, secular, and humane. He urged scientists to enter the public arena, avoiding the pressures of narrow professionalism:

*From the perspective of my own participation in science, I certainly would not tax my colleagues with indifference to human problems. However, I believe that many of them are easily discouraged by larger problems and neglect to search for the ways in which their own expertise might be a unique key to solving a small problem, or perhaps more often to discovering an insidious new one (16).*

Lederberg returned to New York in 1978 as President of Rockefeller University and set that eminent academy on an even steeper climb to excellence. While in New York, he became ever more interested in issues of national security: enrolled as a member of the US Defense Science Board, he advised the government on defenses against bioterrorism, the control of biological weapons and—in keeping with his fear of cant—debunking the military equivalent of fibromyalgia, the “Gulf War Syndrome (5).”

## THE IMPRIMATUR

The New York climate of intense intellectual exchange reinforced three of Joshua Lederberg’s lifelong convictions: he believed in the importance of pure excellence in science, no matter what; in the need for quantitative measures of excellence; and an obligation to make room for risk to achieve it. Perhaps such principles are not unexpected in a graduate of Stuyvesant High School—and a Nobel laureate, to boot.

Personally unassuming, warm, and generous, he was tough as nails when it came to fashionable cant. He praised meritocracy and defended it against the political, financial, and hierarchical enemies of promise. He asked a critical question in one of his early Washington Post essays:

*Not long ago, I received an incredible demand, the more so as it was a formal requirement under United States law. It would compel me to look again at my colleagues and the staff of our university department with the eyes of a bigot to produce a racial census of employees belonging to certain minority groups. The purpose—to help enforce laws that forbid racial bias in employment on Government-aided projects—may be laudable. It is not that purpose but the means, namely calculated racial discrimination, that deserves critical discussion, not only because of its flimsy basis in scientific biology, but more importantly because it is setting the precedents for the kind of society we are building (17).*

Joshua Lederberg founded two very successful, ongoing programs in the development of scientific careers, the Pew Scholars in Biomedical Sciences (18), and the Ellison Medical Foundation (19). His one charge to the selection committees was that each applicant be judged not by geographic, gender, or pigmentary criteria, but by the answer to a simple question: “What’s the discovery?” He also ruled that the proposals be short, innovative, and free of the extensive data-dumps demanded by the NIH.

Lederberg was also a major proponent of quantifying any individual contribution to science, over and above its word-of-mouth reputation. He’d had enough of the days of “personality and race.” Prompted by Eugene Garfield’s 1955 proposal for “Scientific Citation Index (20),” Lederberg soon sent Garfield a supportive letter and promptly a Genetics Citation index was underway. While one or another traditional critic carped at the value of citation rankings, Lederberg and Garfield soon won out: it’s now the universally consulted Web of Science®. Citation indexing has proved invaluable in sorting out the bloodlines of current research and its utility for the republic of letters. Most recently, when the “h factor” was introduced as a means of judging the impact of individual scientists, (21) Josh confided that he was pleased to have come out so well on that score for work done so many years ago. (22)

Lederberg was also convinced that the editing and review of scientific publications was the best means of keeping excellence alive. In 1991 he addressed an international conference of scientific editors at the Marine Biological Laboratory in Woods Hole. His essay spelled out why, how, and what should appear in our literature:

*Above all, the act of publication is an inscription under oath, a testimony . . . I only need to remind you of the term “imprimatur” (a wonderful metaphor): the imprinted witness that, an article having appeared in a refereed journal, it had survived a critical process, a conspiracy if you like, of the editors and the publishers and the referees.*

*It is the essential ingredient to make scientific work responsible in the sense that one cannot readily retreat from assertions that have been signed, delivered to the printer and made available to thousands (2).*

It’s a fine standard and we might say that it constitutes as much of Joshua Lederberg’s legacy as his discoveries of viral transduction or bacterial sex. FJ

### Requiescat in Pace

Gerald Weissmann  
Editor-in-Chief  
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