Biography

Joshua Lederberg, PhD: Nobel Laureate, Geneticist, and President Emeritus of The Rockefeller University

B. Lee Ligon, PhD

In 1958, the Nobel Prize in Physiology or Medicine went to a young man of 33 years of age for his discovery that bacteria reproduce by the mutual exchange of genes and that some viruses carry hereditary materials from one bacterial cell to another. Rather than rewarding the culmination of an individual's career, the Prize represented only the beginning of a long, fruitful, and varied one. The recipient was Dr Joshua Lederberg, whose lifelong research activity has been in the field of genetic structure and function in microorganisms. He went on to become President of Rockefeller University and a vital force in the development of computer technology and policies concerning scientific issues associated with space exploration. In addition to the Nobel Prize and the National Medal of Science, Lederberg has been awarded numerous honorary Doctor of Science and Medical Doctor degrees, as well as the LLD from the University of Pennsylvania. He has been awarded a Foreign Membership of the Royal Society, London, and he holds the rank of Commandeur in the Ordre des Arts et des Lettres of the French Republic. In February 1997, he received the Maxwell Finland Award of the National Foundation for Infectious Diseases. He is an honorary life member of the New York Academy of Medicine and received its John Stearns award for 1996. He is a past chairman and now honorary life governor of the New York Academy of Science. This article provides an overview of Dr Lederberg's life, and in doing so seeks to capture the rich thread of moral and ethical fiber and the deep concern for humanity and the environment that characterize his emphases, products no doubt of the spiritual heritage imparted to him by his devout rabbi father and mother.

"A scientific publication is a grave act to be undertaken with the utmost seriousness; it's an inscription under oath. . . . So you see, I take the literature very seriously. To me it's holy writ *and I want to be sure that, in whatever format it is distributed, it will be accessible, its veracity can be attested by its being observable by everyone at will, and it should be an achievement that cannot be altered." (emphasis inserted)*[1]

Introduction

In 1958, the Nobel Prize in Physiology or Medicine went to a young man of 33 years of age for his discovery that bacteria reproduce by the mutual exchange of genes and that some viruses carry hereditary materials from one bacterial cell to another. He was a corecipient with Edward Tatum and George Beadle.[2,3] Rather than rewarding the culmination of an individual's career, the Prize represented only the beginning of a long, fruitful, and varied one. The recipient was Dr Joshua Lederberg (Fig 1), whose lifelong research activity has been in the field of genetic structure and function in microorganisms.[4] He went on to become President of The Rockefeller University and a vital force in the development of computer technology and of policies concerning scientific issues associated with space exploration. In his writings and other works, a rich thread of moral and ethical fiber and a deep concern for humanity and the environment are interwoven with the scientific data throughout the fabric of the text, products no doubt of the spiritual heritage imparted to him by his devout father and mother. In writing this article, my hope has been to capture that fiber, as well as present a biographical sketch of a man who tremendously impacted the fields of bacteria research and antibiotics. To do so, I unashamedly quote extensively from correspondence, feeling that one's own words are far more adequate in revealing one's character and beliefs than are the feeble attempts of an outside biographer.

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Early Childhood

Joshua Lederberg was born in Montclair, New Jersey on May 23, 1925, the first of three boys born to Rabbi Zwi H. and Esther Goldenbaum Lederberg. The rabbi and his wife had emigrated

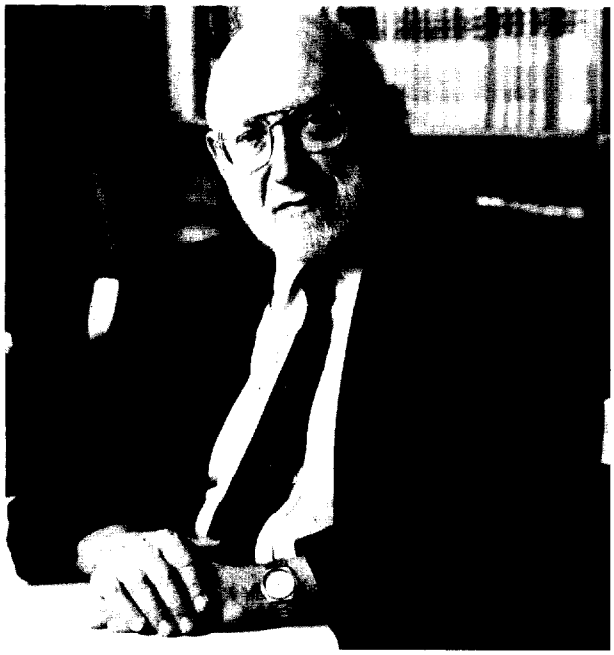

Figure 1. Dr Joshua Lederberg, President Emeritus of The Rockefeller University.

the year before from Israel to New York. His father, a deeply religious man, expected that Joshua, who was his first-born son and who bore the name of the Old Testament figure who led the Israelites into the promised land after Moses' death, would pursue a similar path. However, the younger Lederberg's interests went a different direction. At a very early age, he became interested in scientific and secular matters, his interests being fixed on science by the time he was 6 or 7 years of age and differentiated into biology by the time he was 12 or 13. His earliest recollections "aver an unswerving interest in science as the means by which man could strive for understanding of his origin, setting and purpose, and for power to forestall his natural fate of hunger, disease and death" (personal correspondence, June 18, 1998).

The lad was firm in his convictions. He recalls that the "Jewish reading in Genesis of the expulsion from Eden makes no presumptions of the benignity of Nature. 'By the sweat of thy brow' . . . may have been the most acceptable deviation from the orthodox religious calling of my family tradition. These images were reinforced by the roles of Albert Einstein and Chaim Weizmann as culture heroes—heroes whose secular achievements my parents and I could together understand and appreciate, regardless of the intergenerational conflicts evoked by my callow agnosticism. I could not then see how the monotheistic worldview and the central teachings of the Old Testament, and their ethical imperatives for contemporary life, related to the tribal rituals shaped in the Diaspora . . . Science would be a path to knowledge of the cosmic order. It would also be a means of alleviating human suffering. . . . The Jewish tradition is remarkably tolerant of skepticism. . . . The agnostic set of mind thus permitted, together with my reaction to my father's orthodoxy, carried over into my reflex responses to other sources of authoritative knowledge. This was an integration, not a rejection, of Jewish identity: what could be a more Jewish name than 'Joshua'? and I have always borne it proudly" (personal communication, June 18, 1998). Although the rabbi initially found his son's position disturbing and sought to redirect the boy's interests, he eventually conceded that "there are many ways to follow the Torah" and allowed that "if you want to seek truth through science, that's alright [sic] too."[5,6]

In describing his early interest in science, Lederberg returns to the days when he was being reared in the Washington Heights District of Upper Manhattan, New York City, where he attended the Public School 46, Stitt Junior High School 164, and Stuyvesant High School, which specializes in science.[6,7] As an elementary student, the young Joshua was curious and far advanced for his age, reading at levels that were 5 to 6 years ahead of his grade. The inquisitive youngster was, no doubt, somewhat disruptive, his intelligence and desire to learn being so far beyond those of his peers. He recounts that "I made a contract with some of my teachers that if I didn't ask too many disruptive questions, I could sit and do my own work in the back of the room. . . . But, I was reading medical textbooks when I was 11 to 12 years old." He later learned that he had the highest score in the Northeastern region on standardized IQ tests.[5] He attributes his training to "the individuals who gave so much of themselves as parents, teachers, colleagues, and friends, and to a system that has offered extraordinary nurture to whatever talent and ambition I could bring."[5] He recalls that "New York City at the time thus had a network of institutions directed to enhancing the intellectual and social mobility of its melting pot youth. Generationally, I was fortunately placed: my teachers were already successors to an earlier era of patronizing condescension to the wave of Eastern European immigrants. Many of them were Jewish; all were inculcated with ethnic neutrality, and liberal minded tolerance: attitudes conveyed to their students" (personal correspondence, June 18, 1998).

These were also years of powerful influence from another realm: the political arena. Hitler had achieved power in Germany when Lederberg was 8 years old, "just old enough to have no doubt about the aims of his march across Europe. Eight years of fascinated horror at the unfolding of history followed—the persecution of the German Jews, the flight of intellectuals like Albert Einstein, the occupation of Austria, Munich, the Nazi-Soviet pact and partition of Poland, the fall of France, the victory of the RAF in the Battle of Britain, the Nazi invasion of Russia" (personal correspondence, June 18, 1998). All of these events impressed the youth with both a sense of his heritage and an even stronger desire to discover a meaningful way to relate to life with all its complexities.

Youth and College Education

When he reached Stuyvesant High School, where he first encountered "intellectual sparring partners," Joshua became interested in cytochemistry. Not only did the school attract the keenest minds among young people, it also offered advanced laboratory opportunities that were augmented by the American Institute Science Laboratory. The Laboratory has an interesting history: during the New York World's Fair (that started in 1939), which offered wonderful stimuli, a young psychologist

named Henry Platt, who had a vision of a means of encouraging young scientific minds, happened to meet Thomas J. Watson at the Fair. Platt persuaded Watson to support a laboratory where they could conduct authentic scientific research, with appropriate equipment and supervision. The project materialized as the American Institute of Science Laboratory (AISL). As a reward for the most elegant posters, the AISL offered facilities for the students to conduct original research during their after-school and weekend hours. In the study of cytochemistry, they used, Lederberg recalls, acetic acid and formaldehyde and uranyl acetate and all kinds of poisonous materials, hoping to preserve the details of cell structure.[5,8] One of the many serendipitous moments in Lederberg's life came at the time between his graduation from high school in January and his matriculation into Columbia. Joshua was accepted into the program at the AISL, where he had good facilities and unbroken time to continue the cytochemical work he had started at Stuyvesant. He also began to focus on the chemistry of the nucleolus, which had many of the properties of nucleic acids, but was not consistent with being pure deoxyribonucleic acid (DNA).[5]

Equally important as the schools to his education was the local Washington Heights branch of the Carnegie-Astor New York Public Library system, which "symbolized and embodied the melting pot ideology. My father was an orthodox rabbi, born and educated in Israel, and thus had more prestige, higher intellectual aspirations for his children, and less income than most of his neighbors. Like many other children of Jewish immigrants in New York City of the first quarter-century, I was recruited into an efficient and calculated system of Americanization ... my parents had an uncomplicated appreciation of America as a promised land. My own political ideologies have been more consistent with them than reactive to that belief" (personal correspondence, June 18, 1998). Joshua was an avid reader and was captured by the works of Eddington and Jeans on physics and inspirational works like Jaffe's *Crucibles* in chemistry. He recounts that his perspective on biology and man's place in the cosmos was shaped by Wells, Huxley and Wells' encyclopedic *The Science of Life*. Perhaps his greatest literary treasure was Bodansky's *Introduction to Physiological Chemistry*,[9] a copy of which he received as a Bar Mitzvah (1938) present. It is still on his bookshelf, the pages worn and the print almost gone.[6] It is "a testimony of my firm and precocious interest in biochemistry, crystallized already by my 13th birthday. It was also my covenant with my father, that a career in science would be a redeeming surrogate for the study of the Torah, an alternative approach to enlightenment and truth" (personal correspondence, June 18, 1998).

College Years and Medical School

When the time came for Lederberg to attend college, he applied to Cornell, "on account of Leslie Sharp's presence on the faculty.... But Cornell was in practice open only to wealthy tuition-paying students, or to farm boys who could enroll in the New York State funded College of Agriculture. [His] application for scholarship at Telluride House was rejected" (personal correspondence, June 18, 1998). He thought, too, of City College, but it had limited graduate work and scarcely any research facilities. He chose Columbia University for several reasons that were "motivated by a passion to learn how to bring the power of chemical analysis to the secrets of life." Thomas Hunt Morgan, who had founded modern cell biology and genetics, had been there, as had E.B. Wilson, and the "initiating monograph of cell biology," a classical text entitled *The Cell in Differentiation and Heredity*, had come from Columbia. Also, the university was in New York, providing the added advantage of economical feasibility: he could attend college while still living at home. He was awarded a scholarship that insured his ability to attend Columbia rather than City College.[6]

When Joshua started at Columbia, his course of study was adjusted to accommodate his intense interest in the sciences, and, even as a freshman, he was permitted to register for graduate courses in the Department of Zoology. He was able, then, to pursue his own research, having been given a laboratory desk in the histology laboratory. After his introduction to cytology, he became curious about how the drug colchicine interferes with the mitotic spindle and made his first discovery: an apparent gradient of susceptibility to colchicine down the onion root meristem. This work led to two other research projects: an attempt to induce chromosome aneuploidy in mice by applying limiting concentrations of colchicine during spermatogenesis and a broader investigation of the effects of narcotics and of other specific inhibitors on the mitotic process.[6]

In September of 1942, while searching for courses in cell physiology after becoming intrigued with the cytophysiology of mitosis, Lederberg met Francis Ryan, who was to become his mentor at Columbia. The latter had just returned from Stanford University, where he had completed his postdoctoral fellowship under Tatum. Ryan had arrived at Stanford just shortly after Beadle and Tatum had reported their first findings on biochemical mutants in *Neurospora*, genetically blocked in the biosynthesis of any of a multitude of specific growth factors[10,11] and had convinced them to allow him to work in their laboratory as their first postdoctoral fellow. He had begun his work on *Neurospora* by studying the effects of environmental variables, particularly temperature, on growth and convenient ways to measure it. When he assumed his new position as Instructor in Zoology at Columbia, Ryan introduced the science of *Neurospora* biochemical genetics, which, along with his gift of "inspired teaching," redirected Lederberg's career.[6]

By January 1943, Lederberg had secured a place in Ryan's laboratory, where he assisted in preparing media and handling the *Neurospora* cultures. The involvement in the scientific milieu of that laboratory and at that particular time was a fortuitous event in his life. The experience not only was his first opportunity to observe significant research in action, but it also was a period of intellectual exchange with Ryan and graduate students.[6] Lederberg recounts that "Professor Ryan took a callow underclassman from Washington Heights, brash and argumentative as precocious students often are, and turned me into a scientist."[12] Ryan's willingness to allow him to make room for speculations that went contrary to the common wisdom of the day were the catalyst for what Lederberg frequently calls his serendipitous discovery that later led to his receiving the Nobel Prize. He defines serendipity as "more than good luck of accidental discovery" and, using Louis Pasteur' remark that "chance favors the prepared mind," argues that "the prepared

mind requires unfettered opportunity to recognize and follow unplanned paths . . . when we pursue our passion to master what was once unknowable, we move from a plodding struggle with nature to an ongoing, enlightening conversation. We also then stumble upon the kind of advances that repeatedly justify society's great investment in science."[12] The common opinion that bacteria were "schizomycetes" might still prevail had they not used the unique K-12 strain of *Escherichia coli.* Lederberg frequently emphasizes that he was allowed a freedom of investigation that might be scoffed at today, and because he was going counter to the system, might seldom be granted—with unknown loss of scientific discovery.[12]

At the time he entered Ryan's laboratory, Lederberg was involved in the Navy V-12 college training program, which he had joined when he was 17 years old. The program's premedical curriculum was compressed to about 18 months of instruction, and the 4-year MD curriculum was designed to be completed in 3 calendar years. Lederberg was designated to be a future medical officer, and, had the war continued, would have had an entirely different career. Instead, with the war ending as it did in 1945, he was able to pursue the scientific research he had started.[13] While studying the stool specimens for parasite ova and examining blood smears of malaria among the US Marines returning from the Guadalcanal campaign, Lederberg looked for the chromosomes of *Plasmodium vivax.* Although the chromosomes were so tiny and the staining was so faint that one could not insist on the reality of the observations, the experiments revealed to Lederberg the sexual stages of the malaria parasite and instilled an awareness of the possibility that other microbes, perhaps even bacteria, have cryptic sexual stages.[6]

In October 1944, Lederberg began his medical course at Columbia College of Physicians and Surgeons (P&S), where he continued his research on the control of mitosis. However, the school discouraged research among first-year medical students, so Lederberg retained his intellectual and social connections on the Morningside Heights campus. That same year, Avery, MacLeod, and McCarty of the The Rockefeller Institute made the important biological discovery of the substance responsible for pneumococcal transformation.[14] While bacterial genetics was poorly understood at the time, including some outstanding misinterpretations (see Lederberg for full explanation[6]), the phenomenon could be thought of as the transmission of a gene from one bacterial cell to another. Lederberg knew of the discovery only by word of mouth until January 20, 1945, when he finally got access to the researchers' article. Inspired by the possibilities the research offered, Lederberg began to speculate on the merits of attempting a similar transformation by DNA in *Neurospora:* the organism had a well-understood life cycle and genetic structure and was amenable to selection for rare nutritionally self-sufficient forms that would facilitate the assay for the transformed cells. He approached Ryan, who was working on *Neurospora,* with his idea and was given permission to explore the concept as his first research project under Ryan's direction.[6] By exploiting DNA transformation in an organism with manifest genetic structure, he had hoped to launch the study known today as "molecular genetics."

Although they quickly discovered that the *Neurospora* mutant *leucineless,* which they had from Beadle, would spontaneously revert to prototrophy and that their assay was not reliable for the effect of the DNA in *Neurospora,* the genetic analysis of the reverse-mutation phenomenon resulted in the publication of Lederberg's first paper with Ryan.[15]

The young Lederberg (Fig 2) continued to question the prevailing contention that bacteria were asexual, despite the prevailing consensus that polymorphisms were the results of contaminated cultures and that any consideration that they were purported exhibitions of sexual union between bacterial cells[16,17] were foolish. He was influenced by several scientific factors: the more sophisticated textbooks admitted that little genetic testing of the sexuality claims had been performed and, more enlightening, the sexuality in yeast recognized through the research of Sol Spiegelman and Harriett Taylor was being popularized at Columbia. Lederberg felt that "if bacteria could be crossed, a new repertoire of biological materials for experimental analysis would be available to physiological genetics and biochemistry." Results obtained by Beadle and Coonradt on the nutritional symbiosis in *Neurospora* heterokaryons and their speculations on the role of heterokaryosis in the evolution of sexual reproduction provided the insight that heterokaryosis

Figure 2. Young Lederberg as a pre-med student, December 1945. (Reprinted with permission of The Rockefeller University).

might be found in bacteria—even if full-blown sexuality were not.[18]

While Lederberg was considering all these possibilities, Dubos' extensive review of prior efforts to assess sexuality in bacteria was published.[19] The methods used had been morphological and genetic, but many of the attempts were muddled and the two more clearheaded ones had negative results.[20,21] The review showed, ultimately, that the question of sexuality had never been critically tested. Obscuring genetic testing in bacteriology was the idea that bacteria reacted holistically to environmental insult and that drug or virus resistance was a form of physiological adaptation that could then become genetically fixed. This stance was supported by Sir Cyril Hinselwood, a Nobel-laureate physical chemist and President of the Royal Society, despite the fact that no evidence had been presented and it contradicted the conception framework of population analysis that had emerged for the rest of biology.[6]

The more solid research was shifting the emphasis to the possibility of gene recombination in the natural history of bacteria. The taxonomic tables of the species or serotypes of *Salmonella* lent further support.[22] The subsequent studies reported from this finding led to Lederberg's idea that the numerous combinations of somatic and flagellar antigens were generated by some recombinational mechanism, as well as to speculation of recombination in *E coli.* By using a set of biochemical mutants in bacteria that he collected in Ryan's laboratory, Lederberg began the painstaking process.

Meanwhile, his mentor heard that Tatum, whose doctoral work had been in biochemistry of bacteria, was preparing to move from Stanford University to Yale to establish a new program in microbiology. He recommended that Lederberg apply to work with him directly, which he did, sending him his research plan. Tatum was impressed and invited Lederberg to come to New Haven in March, where he was planning to continue his work in the biochemistry of *Neurospora* while also continuing to follow up on the possibility of bacterial sex.[6] Dean Sevringhaus of P&S approved such a visit as qualifying for an elective quarter offered to medical students during their third year of study, perhaps because he "concurred . . . with [Lederberg's] own private judgment that [he] could make a greater contribution to medicine as an investigator than in clinical practice" (personal correspondence, June 16, 1998). The original plan was for Lederberg to stay at New Haven for only 3 to 6 months and then return to medical school at P&S.[6]

After Lederberg rechecked the stability of Tatum's existing double-mutant strains (eg, 58-161 and 679-183, biotin-methionine and threonine-proline, respectively), they began adding mutations to allow segregation of unselected markers among the prototrophs selected from the mixed cultures on minimal agar medium. By the end of 6 weeks, they had achieved well-controlled, positive results—far beyond their expectations: he had uncovered a system in which two bacteria attach and form a connecting bridge through which the bacteria exchange chromosomal strands. The mechanism was later called "conjugation." By mid-June, they were ready to announce their findings.

Another fortuitous factor in Lederberg's career was the timing: the 1946 international Cold Spring Harbor Symposium, which was upcoming, was dedicated to genetics of microorganisms, and Tatum was already scheduled to talk about his work on *Neurospora.* He and Lederberg were granted a last-minute insertion near the end of the program to report their new results.[23] The presentation elicited lively responses, the most solid arguments coming from Andre Lwoff, who was concerned that the results might be explained by cross-feedings of nutrients between the two strains, rather than exchanged genetic information. Lederberg recounts that his reaction, more heated than necessary, was tempered by the offer of Dr Max Zelle to advise and assist in the direct isolation of single cells under the microscope to quiet the concerns.[6,8] That same year, at the age of 21, Lederberg married Esther M. Zimmer in 1946. She had obtained her MA at Stanford under Professor G.W. Beadle that year. She later (1950) obtained her PhD at the University of Wisconsin. They were married 20 years before separating in 1966.

After the Cold Spring Harbor meeting in 1946, and the one the following year, Lederberg began to receive more support, the first significant confirmations being published by Luca Cavalli-Sforza,[24] with whom Lederberg later developed a close scientific and personal collaboration. Max Delbruck remained the outspoken critic. Lederberg was able to forestall his return to medical studies at P & S another year until September 1947, when he was expected to return to Ryan's laboratory. During that year, they consolidated the preliminary reports and published the first linkage map.[25] Unfortunately, they were not able to show DNA transfer in *E coli,* an accomplishment that would have completed the paradigmatic aims of the experiment.[6]

Ryan and Tatum had managed to procure some partial financial support, and the latter had negotiated with Yale University for Lederberg to have retroactive graduate student registration and de facto enrollment in lecture courses and seminars, with the work performed during 1946 to 1947 serving as his dissertation, it having been defended before an international panel of experts. Although Lederberg also was confronted with retroactive payment of tuition, he was granted the PhD that summer. The PhD degree would prove to broaden his prospects considerably.

University of Wisconsin Years (1947-1959)

Joshua Lederberg's life has been characterized by serendipitous events that changed the course his life goals, as well as the course of science. Such certainly was the case on his receiving the PhD. The anticipated September 1947 arrived, and Lederberg was planning to return to P&S to continue his interrupted medical studies, but again events would take his life in another direction. Just days before his departure for P&S, Lederberg learned that Tatum had been contacted by the University of Wisconsin about an opening in genetics, and Tatum had recommended Lederberg for the position.[6,26] The possibility of his appointment as assistant professor raised some considerable objections—about his age, his research, his character, and his race. At 22, Lederberg was quite young to be given a professorship, and his research with *E coli* was met with much skepticism until Ray Owen provided an extensive review that helped allay some of the university professors' concerns. The personal attributes were no less troubling: Lederberg recounts that

"someone with far stronger suits of tact and polish than mine would have been a more compelling nominee to be among the first Jewish professors in a midwestern college of agriculture. (There have been some happy changes in this country over 40 years. We still have many burdens of fairness in meeting the cries for equity from other groups subject to discrimination.)"[6] Ultimately, the support of R.A. Brink and M.R. Irwin at Wisconsin and E.B. Sinnott at Yale prevailed, and when Lederberg arrived at Wisconsin, he was totally ignorant of the struggle that had ensued in bringing him there.[6]

The possible appointment also posed a personal struggle for the young Lederberg, who was deeply committed to medical research and realized that 2 more years of clinical training followed by another 2 or 3 years of internship and residency would greatly reinforce his medical credentials. But to pursue the medical training would be at the expense of the research at a critically important time, and the Wisconsin position was the only one on the horizon that offered unmitigated support of research in genetics and microbiology. The university was a seat of biochemistry, with its Enzyme Institute, and had a long history of research in genetics and microbiology. Further complicating the matter was that the position was seated in the College of Agriculture, rather than the College of Medicine. So, the decision to go to Wisconsin in 1947 was not made lightly, though Lederberg was convinced that he was founding a new field (there was at the time no field of molecular biology or bacterial genetics) and says today that he has "never had second thoughts about the wisdom of the choice."[6]

A year after Lederberg went to the University of Wisconsin (1948), Norton Zinder arrived. He, too, had known Ryan and, having been frustrated about getting into medical school, had decided to go into research. He came to Lederberg's laboratory as a graduate student who was seeking a field of research. Lederberg steered him toward *Salmonella,* a bacteria closely related to *E coli,* and the prospects of finding a way to cross *Salmonella.* Lederberg himself directed the studies, showing Zinder how to handle *E coli* and ways to be more careful with the *Salmonella* because it was a pathogen. Zinder did the manipulation himself and found instead of conjugation another mechanism, which he and Lederberg termed "transduction"[27]: "the genetically unilateral transfer in contrast to the union of equivalent elements in fertilization."[28] The study led to Zinder's dissertation, and in the early 1950s he went to The Rockefeller University, preceding Lederberg by many years.[26]

In 1952, Lederberg introduced the term "plasmid" to define any extrachromosomal genetic particle.[29] The term was intended to dissipate the controversy concerning whether factors like *kappa* in *Paramecium, sigma* in *Drosophila,* the milk factor for mammary cancer, and other vertically transmitted viruses in mice were "viruses" or "genes." During the 1950s, several ideologies were affecting studies of genetics, among them a theory that cytoplasmic inheritance might be associated with Lysenkist doctrine, which had "criminalized the teaching of Mendelian genetics in the Soviet Union."[30] Lederberg, whose focus in bacterial genetics had been pure Mendel-Morganism, felt that to dismiss a genetic particle as being merely a parasite overlooked an important aspect of cell genetics and biology. His intent was to bring the entire field of endosymbiosis into the consciousness of geneticists.[31] However, for a decade, the term "plasmid" was seldom used, the favored term being "episome," and, although the latter had been carefully constructed to mean agents with traffic in and out of chromosomes, it frequently was used in contexts that ignored or violated the condition of chromosomal habitat. Not until the 1970s did plasmids become important reagents in molecular genetic research and biotechnology. After assuming cardinal roles in the evolution of microbial resistance and of pathogenicity, the usage of the term escalated. For an in-depth review of the history of the term, the reader is directed to Lederberg's recent publication (Plasmid 39:1-9, 1998[31]).

Lederberg remained at Wisconsin for 12 years, where he continued his research on bacterial recombinations (Fig 3). By using recombinant DNA technology, scientists were exploiting the capacity of bacteria to carry plasmids (a term coined by Lederberg to describe the extra rings of genetic material) outside of their chromosomes.[8] The technology had been developed after scientists observed natural recombinant mechanisms in bacteria that involved the crossing over of independent genetic combinations through transformation, conjugation, and transduction. He was promoted to Associate Professor in 1950 and Professor in 1954. In 1957, he organized the Department of Medical Genetics, for which he was Chairman during 1957 to 1958.[8]

In 1957, Lederberg's career took an unexpected turn with the launching of Sputnik. At the time, he was in Australia as a Fulbright Visiting Professor in the University of Melbourne laboratory of immunologist Sir MacFarlane Burnet. In Australia, the satellite was visible for several days before it was visible in the northern hemisphere. His immediate reaction was to realize that with the new experimental tool, precautions were needed. He also was elected that year to the National Academy of Sciences (USA).[8]

When he returned to Washington in 1958, he began to immerse himself in readings on astronomy and rocketry. Concerned with the possibility of contamination of life forms that might be present on other planets, he began a successful campaign to ensure that a doctrine of quarantine for space missions would be instituted to ensure that contamination of life forms was not taken to or brought from Mars or other planets. He recalls that "I was the only biologist at that time who seemed to take the idea of extraterrestrial exploration seriously.... People were saying it would be a 100 years before we even got to the moon."[8] Detlev Bronk and Federick Seitz, officers of the National Academy of Sciences at the time, heeded Lederberg's warnings, and the Academy expressed formal concern by February 1958.

An international committee was formed to establish guidelines and plan methods for detecting and protecting life in space. Because he was among the first scientists to raise the issue, which quickly received considerable attention, he was put in touch with the newly developing space agency. It was completely ignorant about biological issues, so Lederberg organized committees to advise them on biological aspects of the future space exploration, biological science. Recognizing Lederberg's expertise, the space committee suggested that he put his knowledge to work in designing some of the experiments. Ignoring his colleagues' skepticism about space travel, Lederberg proceeded, feeling that if the government were going to

Figure 3. Dr Lederberg in his laboratory at The University of Wisconsin-Madison. Courtesy of University of Wisconsin-Madison Archives; negative 4459-M.

make the sort of enormous investment that appeared to be the case, prudence dictated that he attempt to get the best scientific involvement from it as possible. He was "convinced . . . that once the first satellite was up the timetable would be very short, and my fear was that the space program would be pushed ahead for military and political reasons without regard for the scientific implications."[8] He served on the Academy's committees from 1958 to 1977, as well as on NASA's lunar and planetary mission boards from 1960 to 1977. Unfortunately, at least from Lederberg's standpoint, the direction went toward placing men in space rather than into robotics and computation and other areas that might have produced more scientific data.[8,32]

In 1958, at the age of 33, Lederberg received the Nobel Prize for his research in genetic structures and function in microorganisms. His personal account reveals his humility and surprise. When a Swedish newspaper reporter called to ask his reactions, he could only respond by asking "to what?" Thinking that it might be a practical joke, Lederberg was not persuaded that it was true until after the reporter gave him more information. He recalls that, still not wanting "to take my chances on believing it, and . . . a little concerned that the rumor would get around and prove to be a false rumor . . . I decided to get out of sight for a while until I was absolutely certain. I didn't want to run into people who had congratulated me, and then would not want to face me the next day, when they found out it was all a mistake." Once he got the formal invitation, he and his wife flew to Stockholm, where they were greeted very graciously and enjoyed the week-long festivities.

On the home front, receiving the award posed some problems, however, the news coming as it did in October, 1958, a month after Lederberg had agreed to leave Wisconsin to go to Stanford University. The dilemma was that Wisconsin had somebody leaving who was being awarded the Nobel Prize, and Stanford was not able to enjoy the acclaim because Lederberg was not yet there. In addition, the move posed the difficulty of having to prepare an acceptance lecture at a very inopportune time. He elected to exercise the statute that allowed him to give the Prize lecture within 6 months, so he collected the Prize and returned in the spring to complete the process.[33]

The Stanford Years (1959-1978)

In January 1959, Lederberg left Wisconsin in the middle of a blinding snowstorm for Stanford. The Wisconsin position had provided a framework for grounding in practical applications of biotechnology and associations with important researchers, but, ultimately, Lederberg was to find affiliation with a medical educational and research environment more compelling. When Lederberg was invited to join Stanford University, effective February 1959, concurrent with Arthur Kornberg's move, he saw his opportunity to return to medically-centered research. He took the position, which subsequently led to his move to The Rockefeller University.[6]

His appointment to the medical school faculty offered the opportunity to relate genetics to the wider context of human health and biology, particularly neurobiology and mental illness (Fig 4). These were areas that had intrigued him since childhood, and he had long desired to study them. As Chairman of Genetics, he oversaw numerous studies and helped institute a

Figure 4. Joshua Lederberg in his laboratory at Stanford University. (Reprinted with permission of The Rockefeller University).

human biology curriculum for undergraduates. Having gained insights through the space program into the potential for computers, he formed an alliance with Edward Feigenbaum, Chairman of Computer Science at Stanford, and another computer scientist, Professor Bruce Buchanan and, later, Carl Djerassi, Professor of Chemistry. They created DENDRAL, a computer program for generating structures of organic molecules and exploring analyzing mass-spectrometric data. Further programs in medical diagnosis and disease management were developed with the help of a consultant in infectious diseases. Many years later, it was extended to an experimental design in molecular genetics. In 1974, they established the Stanford University Medical Experimental Computer (SUMEX) with support from NIH. It was designed to provide hardware access for research projects all over the country.

In the early 1960s, Lederberg began serving on various policy-oriented committees, an outgrowth of his involvement on study sections with the National Science Foundation, National Institutes of Health. As he became increasingly interested in arms control, both nuclear and biological, a product of his awareness of the potential threat of biological weapons, he began to address the issues publicly. Recognizing the need for increased public awareness and understanding of science, he initiated in 1966 a weekly column for *The Washington Post.* For over 6 years, the column dealt with numerous topics, including manipulating genes, manipulating weather, science ethics, science education, the environment, the history of medicine, and the state of science reporting itself.[8] At an early date, he was preoccupied with the hazards of new infectious disease outbreaks, and he often dealth with these in his columns.

When the government was trying to negotiate the Biological Weapons Conventions, Lederberg was invited to be an advisor to the arms control administration. The responsibility took him to Geneva between 1970 and 1972, and, to better acquaint himself with public policy and international politics, he began attending seminars at Stanford in the political science department. An outgrowth of those seminars was the organization, along with two nuclear physicists who were actively involved in the nuclear arms control, of an undergraduate curriculum in national security and arms control at Stanford. That formation led to involvement on various committees, as well as the academic critical side, and over a period of 20 years Lederberg developed an expertise in that area as well.

In addition to these achievements and positions as Professor of Biology and Professor of Computer Science, while at Stanford, Lederberg had active memberships in numerous governmental and scientific agencies and commissions, including panels of the President's Science Advisory Committee (Fig 5). He also served on President John F. Kennedy's Panel of Mental Retardation and directed research on the genetics, development, and neurobiology of retardation at the Kennedy Laboratories for Molecular Medicine at Stanford.[8]

The Rockefeller University Years (1978-Present)

In 1978, Lederberg was appointed president of The Rockefeller University (Fig 6). In coming to the University, he was returning to the city of his youth, to the place where, as a child of immigrant parents, he had engaged in "quasi-Talmudic argumentation" with his rabbi father, where he had confounded his teachers with his precociousness, where he had fed his voracious intellectual appetite at the libraries, where he had studied at Stuyvesant High School. It seemed he had come full circle. Indeed, his life, from a literary perspective, would seem to fit the structure of the "quest" narrative: the son of the Jewish rabbi, who had rejected his father's goals for him, had gone on his quest for scientific knowledge as a means for defining life, and was returning victorious with the bounty: tremendous scientific discoveries that would impact the course of the scientific world, public involvement in issues of science that concerned the political world as well as the environment, and the Nobel Prize.[8]

The University also had changed while Lederberg was away. During the 1950s and 1960s, the campus had been expanded and a graduate degree program had been established. But, as often happens with progress, some of the traditional priorities had dissolved. Lederberg's concerns regarding the curriculum and scope were the same as those the board of trustees had been reaching: a need to reemphasize the university's traditional strengths. During Lederberg's administration (Fig 7) most of

Figure 5. Dr Joshua Lederberg, taken in Seattle, 1977. Courtesy of Dr Lederberg.

the new laboratories established were those that concentrate on biomedical investigations and that rely heavily on the insights and methods of molecular biology. Leaders were recruited from around the world, as well as from the University's own faculty. While retaining the commitment to basic research in the biological and physical sciences, the University expanded its thrust to include heart disease, cancer, mental and neurological illness, and infectious diseases, including those of the Third World.[8]

Another concern that Lederberg had to tackle was the need to attract promising young investigators to a city with housing costs that were so high that they precluded some candidates considering Rockefeller. With considerable efforts in planning, revenue management, and fund-raising, by 1989, the university was able to open a new university apartment building, the Scholars Residence, which is located adjacent to the Faculty House. A large laboratory building, part of which is designated for housing of scientists who share joint appointments on the Rockefeller faculty and on the Howard Hughes Medical Institute (which also was established during Lederberg's tenure as president) was established.[8]

In October 1989, Joshua Lederberg received the nation's highest scientific award, the National Medal of Science (Fig 8). No greater award for seeking truth through science was left for the young man, now scholar and scientific leader, who had convinced his father that his pursuits were as worthy as those of the devout rabbi. Certainly, he has fulfilled his goal and his promise.

The "Retirement" Years

In 1990, Joshua Lederberg took mandatory retirement as President of The Rockefeller University, but his work has not slowed. In addition to continuing his research activities there in the field of DNA secondary structure and mutagenesis in bacteria, Lederberg is involved with computers. He chairs a UNESCO committee on how to improve global Internet communication for science and on how to assist people in the Third World obtain access to it.[34]

He continues to address numerous concerns of ethical and scientific issues, the latter having to do especially with emerging pathogens. In 1996, he dealt with the "ever-evolving adversary" that we face in "microbes a billionfold more numerous than ourselves, vested with high-intrinsic mutability and replication times measured in minutes, not years." Arguing for the need for top government policies that give attention to public health, he closed by saying, "Public health generally may be thought of as service to the poor—and well it might—but the stakes are shared by everyone. . . . Further progress will depend very much on 'doctors' recalling and embracing the historic root of that term as docents, ie, teachers."[35] Another concern that Lederberg has addressed recently is biological warfare, which he condemns as "an irresponsible threat against the whole human community."[36]

Today, Joshua Lederberg is the Raymond and Beverly Sackler Foundation Scholar and Professor-Emeritus of molecular genetics and informatics, in addition to being President Emeritus. He also is Chairman of the Laboratory of Molecular Genetics and Informatics. The laboratory focuses on DNA conformation and evolutionary acceleration: how modulation of the secondary and tertiary structure of DNA and its packaging with protein complexes influences its vulnerability to chemical

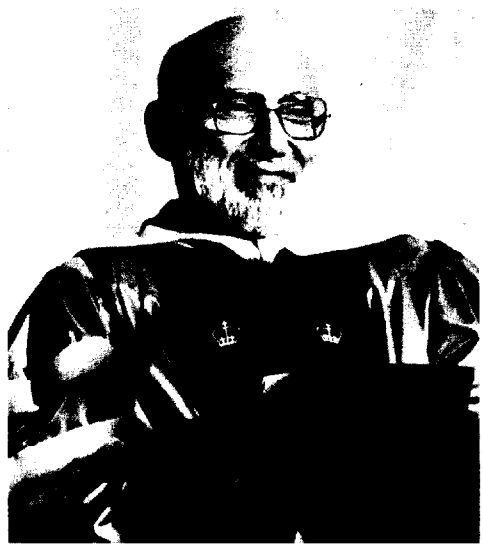

Figure 6. Dr Lederberg invested as President of Rockefeller University. Courtesy of The Rockefeller University Archives.

alteration. Because DNA conformation is a prime actor in the regulation of gene expression, it provides a well-founded mechanism for feedback of environmental circumstances and physiological status to differential mutability of local regions of DNA. In collaboration with the Rutgers Computer Science Department, they also are setting up computer-based systems of reasoning in molecular biology, patterned on the work at Stanford on DENDRAL (1970s). They expect that this logical reconstruction will be of considerable assistance in experiment planning and in organizing and retrieving vast amounts of information recorded in the published literature.[37]

Lederberg also is on the Defense Science Board and involved in numerous ad hoc groups, being very concerned about the use of chemical and biological weapons, as well as the potential for other disasters such as the event that occurred in the Tokyo subway. He has a long-standing interest in international health and is serving a second term on the World Health Organization's Advisory Health Research Council. Recently, he cochaired the study of Emerging Infections, which has appeared under the imprint of the Institute of Medicine.

In addition to the Nobel Prize and the National Medal of Science, Lederberg has been awarded numerous honorary Doctor of Science and Medical Doctor degrees, as well as the LLD from the University of Pennsylvania. He has been awarded a Foreign Membership of the Royal Society, London, and he holds the rank of Commandeur in the Ordre des Arts et des Lettres of the French Republic. In February 1997, he received the Maxwell Finland Award of the National Foundation for Infectious Diseases. He is an honorary life member of the New York Academy of Medicine and received its John Stearns award for 1996. He is a past chairman and now honorary life governor of the New York Academy of Science.

Figure 7. Dr Joshua Lederberg when he was President of The Rockefeller University. (photo by Ingbert Grüttner; reprinted with permission of The Rockefeller University).

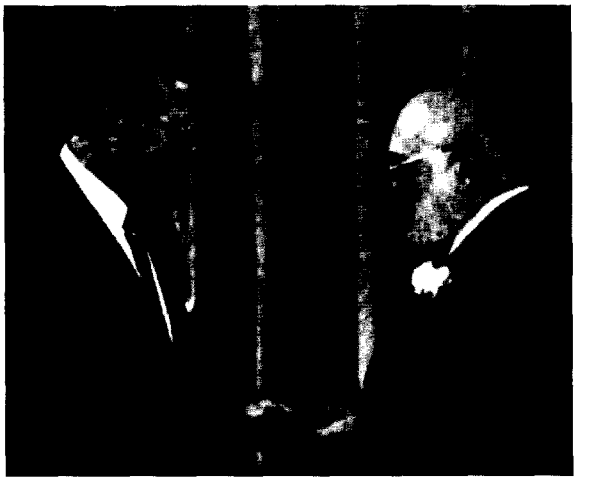

Figure 8. President George Bush presenting Joshua Lederberg the Presidential Medal of Honor, 1989. (photo by Robert Reichert; reprinted with permission of The Rockefeller University).

He lives in New York with his wife, Marguerite Stein Lederberg, who was born in Paris, educated as a physician in the United States, and serves as Clinical Professor of Psychiatry at Memorial Sloan Kettering Cancer Center in New York. They have two children, a son and a daughter.[38]

True to his father's apparent wishes in naming him Joshua, Dr Lederberg has "led" his people through lands of scientific discovery and promise, and today he upholds a moral and ethical standard for humankind.

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