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JOSHUA LEDERBERG
1925—2008

A Biographical Memoir by

S. GAYLEN BRADLEY

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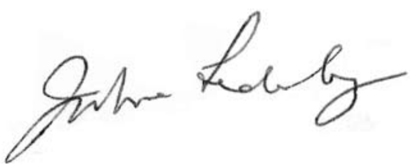
Biographical Memoir



JOSHUA LEDERBERG

May 23, 1925–February 2, 2008

BY S. GAYLEN BRADLEY

JOSHUA LEDERBERG'S PIONEERING work on genetic recombination in bacteria propelled the field of molecular genetics into the forefront of biological and medical research. His discoveries became the foundation for genetic engineering, modern biotechnology, molecular biology and medicine, and gene therapy. After receiving the Nobel Prize in 1958 at the tender age of 33, Joshua Lederberg used his prestige and breadth of knowledge to engage the public and policy makers for five decades in discourses on the consequences of the applications of science. He recognized the potential of computers for the analysis of scientific data, and how the logical processes of scientific induction were applicable to the construction of intelligent computer programs. He collaborated with scientists across many disciplines to revolutionize the applications of computers to chemistry, medicine, and information technology.

While president of Rockefeller University he continued his advocacy for scientific understanding,[1] drew attention to the threat of emerging infectious diseases, and ultimately returned to the laboratory to explore the process of gene mutation. At the time of his death Joshua Lederberg was University Professor and president emeritus of Rockefeller University. He died from pneumonia February 2, 2008, at

New York-Presbyterian Hospital. Surviving him are his wife, Marguerite Stein Kirsch Lederberg; his children Anne Lederberg and David Kirsch; two grandchildren; and his younger brothers Seymour and Dov. His first wife Esther Zimmer Lederberg predeceased him, dying in December 2006.

In undertaking preparation of a memoir Joshua Lederberg cautioned us as biographers that history is an "accounting that begins when the witting participants are gone and unable to contradict the inventions of those who had not participated in the events, and must rely on extant fragments of evidence."[2] Garfield (2008) correctly observed, "He treated documentation of the scientific literature in the Talmudic tradition in which he was raised—as a sacred obligation." I would add that Josh also left extensive documentation of his legacy,[3] noting, "My memory is not perfect; and while I believe I have a far more complete archive of my papers, correspondence, etc. than most of my peers, this is often incomplete on some crucial details."[2]

Joshua Lederberg was born May 23, 1925, in Montclair, New Jersey, the son of Zvi H. Lederberg, an Orthodox rabbi, and Esther Goldenbaum Schulman Lederberg. His parents had emigrated from Palestine to the United States the year before. He was reared in the Washington Heights District of Upper Manhattan, where he attended Public School 46 and Stitt Junior High School 164. He graduated at age 15 from Stuyvesant High School in New York City. His interest in biological science was whetted by Paul de Kruif's book *The Microbe Hunters.*

During his college years, he was allowed to register for graduate courses and to conduct independent research projects. In 1942 Josh met Francis J. Ryan who had recently joined the zoology faculty at Columbia University as an instructor. Josh worked part-time in Ryan's laboratory, preparing culture medium and propagating strains of the orange bread mold *Neurospora crassa*. Josh recounted, "Professor Ryan took a callow underclassman from Washington Heights, brash and argumentative as precocious students often are, and turned me into a scientist" (Ligon, 1998). Josh received his bachelor's of arts degree in zoology/premedicine from Columbia College in 1944, and continued his studies at the College of Physicians and Surgeons of Columbia University Medical School under the V-12 and Hospital Corps accelerated program of the U.S. Navy to train physicians. During this period, he continued to carry out part-time research on *Neurospora*.

Josh had become aware of research on the transfer of bacterial genes by nucleic acid preparations and persuaded Ryan to allow him to pursue this in *Neurospora*. The nutritional mutants of *Neurospora* were not stable, but he and Ryan were able to complete a study on reverse mutations, which was published in the *Proceedings of the National Academy of Sciences* in 1946. After a series of disappointing experiments to demonstrate transfer of genetic information by nucleic acid preparations, Ryan encouraged Josh to apply to the Department of Microbiology and Botany at Yale University to pursue a genetics project with bacteria under the direction of Edward L. Tatum who had recently relocated from Stanford University.

The original plan was for Josh to spend three to six months at Yale University and then return to Columbia's Physicians and Surgeons Medical School. Within six weeks, using nutritional mutants of *Escherichia coli* K-12 that Tatum had prepared, Josh conducted experiments establishing that gene transfer occurred in bacteria (Zuckerman and Lederberg, 1986). The initial reports in 1946 and 1947 were not universally accepted, it being argued by senior international authorities that the results could be attributed to exchange of released nutrients by the mutants, coupled with back mutation during the resulting limited growth. Max Zelle from Cornell University in Ithaca, New York, proposed that the issue be resolved by studies on single cells isolated by micromanipulation, a task that was not completed until 1950.

Josh did not return to medical school but Columbia awarded him an honorary doctorate in 1967. After World War II, the GI Bill was in full operation, and the perceived need for a military-sponsored accelerated physician-training program had passed. After devoting two years with Tatum at Yale University in research that was building a new foundation for bacterial genetics, Ryan and Tatum convinced their academic administrators to award graduate credit for Josh's prior studies and work at Columbia's Physicians and Surgeons Medical School and at Yale University. Josh was obliged to assume the financial obligation for retroactive tuition to establish his academic residence at Yale University. Josh was awarded his Ph.D. degree with Tatum as his research adviser at Yale University in 1947, and an honorary doctorate in 1960.

Josh was faced with many challenging decisions: recently married, in debt, the possibility of returning to medical school, and the potential loss of one of his key mentors, Tatum, who was negotiating a return to Stanford University. Tatum learned of and recommended Josh for a position in genetics at the University of Wisconsin in Madison. Until that time Josh had always envisioned himself as a medical scientist, and the idea of an appointment in the College of Agriculture was not particularly appealing. Moreover Josh, reared in New York as the son of an Orthodox rabbi, was apprehensive about relocating to the Midwest, where he would be separated from his cultural support system and mentors. Though not a practicing Jew as an adult, Josh deeply felt his connection to Judaism, and was delighted several decades later to receive honorary doctorates from Yeshiva University (1970), Mt. Sinai University (1979), the Jewish Theological Seminary (1979), and Tel Aviv University (1991).

Josh was filled with confidence that he was creating a new field and was drawn to the faculty of the University of Wisconsin, which included scientific giants such as enzymologists David E. Green and Henry A. Lardy and geneticists such as Royal Alexander Brink and M. R. Irwin; and the College of Agriculture offered financial support through its resources and those of the Wisconsin Alumni Research Foundation. There were trepidations on the University of Wisconsin side: could a young New Yorker with a yen for medical research adjust to an agricultural college in America's heartland; and should the faculty offer a position to a 22-year-old with dubious academic credentials based upon research that was still questioned by many authorities in fall of 1947?

These skepticisms continued to be expressed during the dissertation research by Josh's wife, Esther Miriam Zimmer Lederberg. Esther had received her master of arts degree at Stanford University in 1946, under the direction of George W. Beadle, and then returned to New York City to work with Norman Giles at Yale University on *Neurospora.* There she met and married Josh and they moved to Wisconsin in the span of one year. An interesting coincidence noted by Tatum in his Nobel lecture is that Esther Zimmer assisted in the isolation of the *Escherichia coli* K-12 nutritional mutants at Stanford University that were used by Josh and Tatum at Yale University. In Madison, Esther entered the graduate program in bacteriology at the University of Wisconsin, pursuing research on the genetic control of mutability in the bacterium *Escherichia coli.* She completed her Ph.D. degree in 1950.

WISCONSIN AND THE GOLDEN AGE OF BACTERIAL GENETICS

Joshua Lederberg joined the faculty of genetics at the University of Wisconsin in Madison as an assistant professor in the fall of 1947. His research career began before the era of big science. Indeed, his early work was funded piecemeal and at a very modest level. The Wisconsin Alumni Research Foundation initially funded his research and the University of Wisconsin Graduate School provided support for his graduate students. By 1954 he had received a contract from the Atomic Energy Commission and an extramural grant from the National Cancer Institute. A number of his trainees were supported by fellowships from the National Science Foundation and the National Research Council. He advanced rapidly through the academic ranks, becoming an associate professor in 1950 and a full professor in 1954.

Josh, having been imprinted with the desire to do medical research, was sympathetic to the application of Norton Zinder for graduate study in genetics, both because Zinder had unsuccessfully aspired to enter medical school and because he had been recommended by Francis Ryan. Zinder joined the laboratory in the fall of 1948, and was immediately steered to a project on *Salmonella typhimurium*, with the expectation that bacterial conjugation in *Escherichia coli* could be extended to include this closely related pathogen. The laboratory was ill suited for work with pathogenic bacteria, and Josh was perhaps not the most dexterous bacteriologist I have known. Nevertheless, Zinder in a relatively short period was able to isolate single mutants and complete the standard conjugation experiment. The promising results led to the demand for double nutritional mutants, with somewhat confusing results. There were many twists and turns as Zinder and Josh ruled out back mutation, complementary cross-feeding of nutrients, and even the need for actual cell contact. Ultimately the critical bacteriophage vector was discovered, and the mechanism of generalized genetic transduction, that is, the unilateral transfer of a limited number of genes by a viral vector, began to unfold. Josh received the Eli Lilly Award as the outstanding young bacteriologist, presented at the Society of American Bacteriologists annual meeting in 1953.

Concurrently there was a swirl of controversy about the process of bacterial conjugation. The Lederbergs, in cooperation with their longtime friend Luigi Luca Cavalli-Sforza, found that the asymmetry in bacterial recombination was controlled by a fertility factor on the cell surface that was readily transmissible. M. Laurance Morse, a mature student with a master's degree and work experience at Oak Ridge National Laboratory, came to Josh's lab as a graduate student, proposing to work with lambda phage. Esther Lederberg by this time had described the K-12 variants of *Escherichia coli* that were lysogenic, sensitive, and resistant to lambda phage. It was also known that the locus for maintaining the lambda genome was linked to the galactose locus. Morse suggested that it would be possible to use induced lambda phage to transfer the galactose locus to lambda sensitive *E. coli.* Indeed, Morse, Esther Lederberg, and Josh developed the gene transfer system that continues to underpin molecular genetics and genetic engineering. Josh clearly understood the implications of this discovery and anticipated that parallel systems would be developed for gene therapy in humans.

By the 1960s Josh was an established senior scientist who was serving on study sections of the National Science Foundation and the National Institutes of Health. Josh recognized the need to improve communication among scientists, the general public, and the private sector.[1] Josh was elected to the National Academy of Sciences in 1957 and he received a Fulbright Visiting Professorship to go to Frank Macfarlane Burnet's department at Melbourne University in Australia, expecting to spend a few months exploring influenza virus genetics.

Josh arrived to find that Burnet had redirected all research in the Walter and Eliza Hall Institute toward immunology. Gustav Joseph Victor Nossal, a new medical graduate, had planned to start a virology project for his Ph.D. degree. Josh and Nossal were thrown together to develop a project on immunology. This provided Josh with the opportunity to address a truly biomedical question, the onset of the immune response, by collaborating with Nossal to test Burnet's theory of clonal selection of antibody producing cells. Josh used his knowledge on antigenic phases of bacterial flagella and his experience with single cells under the light microscope to develop with Nossal a direct experiment to test if individual antibody-producing cells produced one or more antibody specificities. They labored through 62 antibody-producing cells and found no cell that produced more than one antibody specificity.

The experience in Australia had a second profound effect on Josh. The Soviet Union launched the satellite *Sputnik,* which was visible in Australia for several days before it was seen over the United States. Josh immediately recognized that this provided a new tool to understand the Universe, and at the same time posed the threat of cross-contamination of life forms. Upon his return to the United States, Josh persuaded Detlev Bronk and Frederick Seitz of the National Academy of Sciences to express officially a concern about interplanetary cross-contamination.

Josh was intrigued about the possibility of extraterrestrial life ever since he had listened to H. G. Wells's radio broadcast of "War of the Worlds" in 1938 (Lederberg, 1987). In particular, he wanted to test the hypothesis by Svante Arrhenius that life arrived on Earth from bacterial spores traveling through space. Harlyn Halvorson was working on the germination of bacterial spores at the University of Wisconsin, so Josh contacted Halvorson about collaborating on an experiment to determine whether spores could survive exposure to outer space. Josh and Halvorson designed a miniaturized apparatus that would unwind a tape to which spores could attach, and after a time, rewind the strip and spray it with germinating agents. The refractive index of the exposed tape was to be measured to detect changes characteristic of germinating spores. They prepared and submitted a grant request to the U.S. Air Force. At the same time, Josh was advocating that this type of research should be conducted by a civilian agency not the military. Josh and Halvorson ultimately heard from the Air Force that while they liked their proposal, the authority to conduct these experiments had been given to a new agency, and this particular experiment was never carried out (personal comments, Harlyn Halvorson, e-mail, Feb. 16, 2008).

Georges Cohen from the Pasteur Institute came to the University of Wisconsin to spend 1958 in Halvorson's laboratory. While in Madison, Cohen suggested that Dean B. Cowie of the Carnegie Institute of Terrestrial Magnetism be invited to give a seminar. Halvorson hosted a party for Cowie, and Josh was invited. During the evening, Josh asked Cowie what he was working on, and Cowie replied that he was designing an experiment to capture particles in space, place these on Petri dishes, and look for spores. Josh suggested that he collect Moon dust, which had been collecting particles for eons. Cowie asked Halvorson for a slide rule, and disappeared for several hours, emerging to say: you have me beat by 10^{14}. The next few hours were spent on how to collect Moon dust (Lederberg and Cowie, 1958). Someone mentioned that the Soviet Union was sending dogs into space and if one of these landed on the Moon, it would contaminate the Moon. Josh and Cowie immediately drafted a letter, which they sent to *Science* and the *New York Times*, urging that all spacecraft be first sterilized (pers. comm., Harlyn Halvorson, e-mail, Feb. 16, 2008).

Josh had a great influence on the students and faculty at Wisconsin. James F. Crow said that "during the first few years here he was far and away the most important intellectual influence in my life" (Anonymous, 2005). His course in microbial genetics was widely respected and attended by postdoctoral trainees and faculty from the entire Madison campus as well as by graduate students. Josh required the auditors to take his examinations along with the students, a requirement not entered into lightly by his faculty peers. Josh's microbial genetics course addressed segregation in fungi and ill-defined variation in a range of microorganisms as well as the current state of gene transfer in bacteria. His laboratory was a magnet that attracted visiting scientists and guest workers worldwide, such as Sydney D. Rubbo from the University of Melbourne, Luigi Luca Cavalli-Sforza from the Istituto Sieroterapico Milanese "Serafino Belfanti" in Milan, and the immunogeneticist Ruggero Ceppellini from the University of Turin. The University of Turin awarded an honorary doctorate to Josh in 1969.

Josh increasingly felt the need to be associated with the medical school and encouraged John H. Bowers, dean of the University of Wisconsin Medical School to develop a program in medical genetics, which it did in 1957 with Josh as its founding chair (Lederberg, 1997). The Rockefeller Foundation provided funding for three years to launch the program, and Josh enthusiastically set out to expand the department and to offer research opportunities for medical students. The university was not immediately forthcoming with funding for new faculty positions, and Josh began to entertain seriously offers from elsewhere, in particular Stanford University, which was poised to expand research in its medical school. In his letter of resignation Josh wrote to University of Wisconsin president and biochemist Conrad Elvehjem, "Genetics and biochemistry are rapidly converging on the fine structure and biosynthesis of nucleic acid" (Halvorson, 2007). Josh had done almost all the work leading to his share of the Nobel Prize at Wisconsin, and he was leaving for Stanford University in 1958 during the interval between notification and presentation of the prize. To acknowledge the support that the University of Wisconsin had provided for the research honored by the Nobel Prize, Josh donated the gold medal to the regents of the University of Wisconsin. With a sense of a renewed mission to pioneer new biomedical fields, Josh moved on, rarely looking back at the fields he established.

STANFORD AND EXPANDED HORIZONS

Joshua Lederberg and Esther left Wisconsin during a severe snowstorm to relocate to the mild climate of Palo Alto, California (Ligon, 1998), and he rarely returned except to accept an honorary degree from the University of Wisconsin in 1967. Josh had evolved away from being "pushy and disinclined to observe social niceties," into a confident, poised 33-year-old who had learned the value of social graces. Josh was driven by a strong social conscience, nurtured by a father whose faith coexisted with a broad humanist consciousness and a tolerance for divergent views, and by the example of his youngest brother, Dov, who had become a Chabad student and later an artist using computer-generated spiritual images to express Jewish mystical teachings and meditation.

Not fulfilled by success in basic biological science, Josh felt the need to improve the lot of humankind. The opportunity to return to a research-intensive medical school environment was attractive and was reinforced by the strong tradition of Stanford University, where his most important mentors had spent significant portions of their careers. In addition, Josh did not enjoy refining the details of recombination in bacteria and the clash of personalities of newcomers to the field, who were trying to establish their reputations as leaders in the field. Bernard D. Davis (1987) noted the collegial spirit of Josh and the pioneers of microbial genetics, and observed that the workers in the field became intensively competitive over time. Josh told Barbara Hyde in a 1992 interview, "We urgently need to dispel the idea that the primary motivation of researchers is to beat their competitors. I firmly believe that idealism and the excitement of discovery are necessary parts of science" (Lederberg, 1992).

Stanford University's medical school was moving from San Francisco to Palo Alto in 1958, and was on a campaign to recruit outstanding scientists. Among the first new hires were Arthur Kornberg and Joshua Lederberg. At Stanford Josh took on more administrative duties and his extracurricular activities expanded. Josh was commissioned to create a department of genetics, and was named professor and executive head in 1959. Leonard Herzenberg (2006), on the occasion of his Kyoto Prize Commemorative Lecture, acknowledged that his experiments with mammalian cells were largely inspired by Josh's work on bacterial genetics. He commented, "So, I was doubly delighted when Dr. Lederberg took an interest in my work and invited me to join the new genetics department he was founding at the Stanford University School of Medicine."

The move to Stanford University was a watershed in Josh's scientific career. Heretofore Josh had been the master of the insightful bare-bones approach that attacked the foundation of the scientific problem. Stanley Falkow observed,

> Josh was a remarkable man with a remarkable intellect. In terms of policy matters and the '"big" issues of science he was extraordinary. I was always interested though in the fact that he was not by nature an experimental

scientist. My mentor Lou Baron worked with Josh and told me that Josh's rule was that if an experiment required more than 6 Petri dishes and four pipettes, Josh felt it was over–designed. He was surely right that simple experiments are the key but occasionally one needs a bit of technology. Technology is not necessarily good science but good science without good technology is quite difficult (pers. comm., e-mail, Feb. 21, 2008).

At Stanford much of Josh's creative effort was directed toward collaborative work with intellectual peers in chemistry, engineering, and computer science. Carl Djerassi recalled,

When I came to Stanford in 1960, Josh was probably my closest friend, professionally and personally, and within about two years we started to collaborate, I as a chemist, he as a person who works in every field conceivable, including even chemistry (Shortliffe and Rindfleisch, 2000).

Edward A. Feigenbaum had an experience parallel to that of Djerassi,

When I arrived at Stanford in January 1965, I discussed with Josh my goal of creating models of the thinking processes of scientists, especially the processes of empirical induction with which hypotheses and theories were inferred from data. What I needed was a specific task environment in which to study these issues concretely. Josh suggested a task of inferring organic chemical structures from mass spectral data and enthusiastically entered a collaboration (Shortliffe and Rindfleisch, 2000).

The computer software that resulted, called DENDRAL, marked the start of the field of expert systems. It was the goal of Josh and his collaborators to apply the principles and methods of artificial intelligence research to real-life problems in biomedical discovery and clinical practice. The META-DENDRAL program was the first machine-learning program to discover (on its own) new and publishable knowledge in an active (albeit narrow) area of science. The last effort in the collaboration was MOLGEN, a pioneering software development in an area now intensely studied and used: computational molecular biology. The MOLGEN software matched DNA sequences and searched for specific features in the sequences. Other software of MOLGEN aided experimenters in planning recombinant DNA experiments (Buchanan, 2008). For his interdisciplinary work involving computer science, the Association for Computing Machinery awarded him their prestigious Allen Newell Award in1995.

"In parallel with all this computer science research, he chose to take on the role of Prometheus in bringing to the Stanford Medical School the fire of modern computing, both in spirit and in substance (the pioneering ACME time-sharing computer system; and SUMEX-AIM, the first biomedical-oriented computer on the ARPAnet, precursor to the Internet)" (pers. comm., Edward Feigenbaum, e-mail, Apr. 16, 2008). For all his work in biomedical computing the American College of Medical Information awarded Josh its highest award for lifetime achievement, the Morris R. Collen Award, in1999.

During this period, he was also serving as a consultant on health care policy to John F. Kennedy's transition team and on the President's Panel on Mental Retardation. In this latter role he met and earned the respect and confidence of President Kennedy's sister and brother-in-law, Eunice and Sargent Shriver. The Shrivers, deeply interested in the neurological and genetic causes of mental illness, established the Joseph R. Kennedy Jr. Laboratory for Molecular Medicine at Stanford University. Josh became director of the Kennedy Laboratories for Molecular Medicine in 1962. He was also increasingly concerned about the public's understanding of science and committed to writing a weekly column for *The Washington Post* from 1966 to 1971. In these articles he addressed a range of topics, from population control to cloning to scientific ethics to space biology.

Josh continued his interest in space, and served on the lunar and planetary mission boards of the National Aeronautics and Space Administration from 1960 to 1977 and as an intellectual contributor and adviser to the Viking Mission to Mars. Josh argued passionately that it would be more cost-effective to use technology for space exploration rather than manned missions. In particular he expressed concern about the reciprocal infection of planets by agents carried on spacecraft. He was an advocate for worldwide reduction of nuclear weapons and warned of the potential use of biological and chemical agents by extremists. Josh was an adviser to the arms control administration that was negotiating the Biological Weapons Convention and made several visits to Geneva during 1970-1972. Josh also spoke openly about the need for arms control and measures to prevent the proliferation of nuclear and biological weapons.

Esther Lederberg remained dedicated to bench research while Josh became increasingly engrossed in global issues. This divergence in interests contributed to their divorce in 1966. Esther continued at Stanford becoming director of the Plasmid Reference Center, and Josh focused his energies on exobiology, information science, and public policy. In 1968 Josh married Marguerite Stein Kirsch, who was born in Paris and had lived as a refugee in southern France during World War II. After the War, she immigrated to the United States, was educated at the Lycée Français de New York, Bryn Mawr College, and Yale University Medical School, and later became a psychiatrist. Marguerite had a son, David Kirsch, born in 1964, from her first marriage. Marguerite was engaged in the private practice of psychiatry, served as a clinical instructor of pediatrics, and director of the Office of Women's Affairs at Stanford Medical School. Josh and Marguerite had one daughter, Anne, born in 1974.

BACK TO NEW YORK

Josh became president of Rockefeller University in 1978 and served in that capacity until he retired in 1990. He became an active member of the New York Academy of Sciences, and was in quick succession made an honorary life member in 1980 and honorary life governor in 1982. He was named an honorary fellow of the New York Academy of Medicine in 1981. During his dozen years as president, he directed his energies into recruiting resources and scientists to conduct world-class research, using the tools of molecular biology to address problems with medical applications. His achievements earned him further international recognition by being named a foreign member of the Royal Society of London in 1979 and the breadth of his scholarship brought accolades such as fellow of the American Association for the Advancement of Science (1981), fellow of the American Philosophical Society (1982), election to the American Academy of Arts and Science (1982), and recipient of the U. S. National Medal of Science (1989). Additional honorary degrees were bestowed upon him: University of Pennsylvania (1979), Rutgers University (1981), New York University (1984), and Tufts University (1985). Throughout his tenure at Rockefeller University, Josh served on many governmental advisory committees, which for his entire career spanned nine U.S. presidential administrations. Upon retirement as president of the university, he assumed the role of Raymond and Beverly Sackler Foundation Scholar and head of the Laboratory of Molecular Genetics and Informatics, where he once again challenged his nemesis, mutation, with new experimental tools and insight. He focused on how activation of genes affects their susceptibility to mutation. Josh's final contribution to the scientific literature addressed the proposition "that the growth rate of bacteria may not be only determined by factors of nutrition and the environment, but that it might be 'self controlled' in bacterial populations by cellular communication or quorum sensing" (Nackerdien et al., 2008).

Stephen S. Morse stirred Josh's interest in emerging infectious diseases at a Rockefeller University reception in 1987. After several exchanges with Morse, Josh concluded, "The problem of emerging viruses is one that must be addressed at the highest levels" (Morse, 2008). He used his influence to make all governmental agencies, nationally and internationally, aware of the potential threat, serving as chair of a committee of the National Academy of Sciences and as a consultant to the National Centers for Disease Control and Prevention. In 2001 Josh testified before the U.S. Senate Committee on Foreign Relations on biological warfare, asserting that "per kilogram of weapons, the potential lives lost approach those of nuclear weapons, but less costly and sophisticated technology is required." He concluded, "Studies of hypothetical scenarios document the complexity of managing bioterrorist incidents and the stress that control of such incidents would impose on civil order." He argued that first responders needed more training to cope with attacks by extremists. In 2004 Josh in the Rhoda Goldman Health Lecture to the University of California, Berkeley, Goldman School of Public Health observed, "We are at a greater risk today in a globalized world than we were in 1918" (Anonymous, 2004). He went on to caution that "the U.S. should be concerned with such epidemics not only because it would be a 'betrayal of humanity' if we did not, but we should also be concerned for our own safety and security, if such 'diseases are so rampant.'" His other, closely related great passions were the threat of bioterrorism and disarmament of all weapons of mass destruction—nuclear, chemical, biologic. Josh was apprehensive that the goals of political extremists are to interrupt regular normal life and influence policy through megaterrorism (pers. comm., Alexander Keynan, e-mail, Apr. 14, 2008).

Josh broadened his interest in computer modeling of scientific reasoning and bioinformatics. This brought him into close collaboration with colleagues at the National Library of Medicine, which was cataloging his extensive archives,[2] and provided him with the opportunity to hone his wordsmithing skills with interested and able associates. Alexa T. McCray of the Lister Hill National Center for Biomedical Communications observed in a footnote to a 2001 article in the *The Scientist* coauthored with Josh that "he has played the neological game himself with entries like plasmid, exobiology, euphenics, and prototroph."

Josh also coined the term "'microbiome' to signify the ecological community of commensals, symbiotic, and pathogenic microorganisms that literally share our body space and have been all but ignored as determinants of health and disease" (Lederberg and McCray, 2001). Josh's early fascination with information science led him to propose by analogy to binary units (bits) the terms "mits" for mutational units or genes, "rits" for recombinational units or genes, and "phits" for physiological units or genes. He also proposed the term "eugram" for electron mail. Josh anticipated that there would be controversy about the applications of genetic technology in medicine and introduced the term "euphenics" to contrast with eugenics, which had taken on a negative connotation. He was proposing interventions that restored the health phenotype, as distinct from interventions that altered the genotype.

Awards during Josh's retirement years illustrate the breadth of his scientific contributions: Commandeur, L'ordre des arts et des lettres, République Française (1993), the Maxwell Finland Award of the National Foundation for Infectious

Diseases (1997), Honorary Doctor of Military Medicine from the Uniform Services University of the Health Sciences (1998), and the capstone Presidential Medal of Freedom (2006).

Joshua Lederberg not only changed the course of life science but also changed the lives of his associates. Josh did not fear to go where no one had gone before. He had the ability to see the answer to a problem, buried in a vast literature. His personal experimentation was direct and simple, but he readily entered into collaborations calling for sophisticated technology. Josh understood the theoretical and applied implications of his discoveries, and his vision extended far into the future. Above all, Josh was a man of passion for science, and was driven to improve the lot of humankind. His commitment to his father that "science like religious study, offered a path toward enlightenment and truth" was fulfilled.[4]

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1. J. Lederberg. Research and the culture of instrumentalism. 1995. http://www.columbia.edu/cu/21stC/isue-1.1/nobel.htm. Accessed Feb. 2008.
2. Darwin-L Message Log. Academic discussion on the history and theory of the historical sciences. 1994. http://rjohara.net/darwin/log/1994/9409. Accessed Feb. 2008.
3. Finding aid to the Joshua Lederberg papers, 1904-2003. http://profiles.nlm.nih.gov/BB/. Accessed Apr. 2009.
4. As noted in the narrative, Josh left an extensive archives and worked with colleagues to assemble the Joshua Lederberg Papers as one

of the projects of Profiles in Science of the National Library of Medicine. http://profiles.nlm.nih.gov/BB/Views/Exhibit/narrative/biographical.html. Accessed Feb.-Apr. 2008.

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